Unique

Understanding Chromosome & Gene Disorders

15q deletions between 15q15 & 15q22

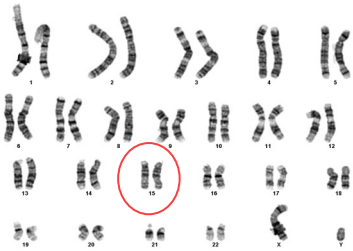
rarechromo.org

15q deletions

A chromosome 15q deletion is a rare genetic condition in which there is a missing (deleted) copy of part of the genetic material that makes up one of the body's chromosomes - chromosome 15. As with other chromosome disorders, having a missing piece of genetic material may affect a child's health, development and intellectual abilities and can be associated with a range of other individual features, to a varying degree. It is important to remember that the outcome of having a 15q deletion is variable and depends on a number of factors, including what and how much genetic material is deleted.

Background on chromosomes

Our bodies are made up of trillions of cells. Most of these cells contain a set of around 20,000 genes that carry the set of instructions that tell the body how to develop, grow and function.



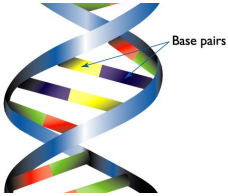
Chromosome pairs 1-22, X and Y (male). Chromosome 15 pair circled in red

Genes are carried in structures called chromosomes, which consist of a complex chemical called DNA. Chromosomes (and hence genes) usually come in pairs, one inherited from the mother and one from the father.

Apart from the sex chromosomes (usually two Xs for a girl and an X and a Y for a boy), chromosomes are numbered 1 to 22, approximately from largest to smallest.

Looking at chromosome 15

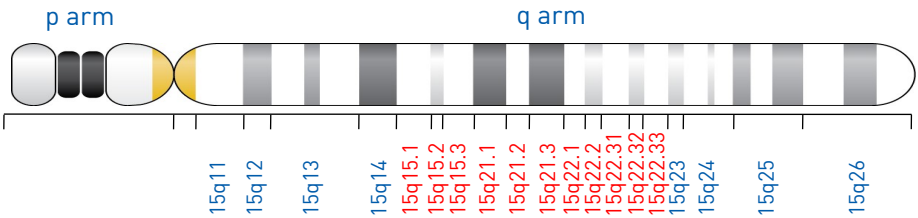
Each chromosome contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. There are millions of base pairs in every chromosome, and they are often counted in millions, where 1 Mb equals one million base pairs. The whole of chromosome 15 has about 102 Mb (102,000,000 base pairs), and approximately 600 genes.



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

Each chromosome has a short (p) arm and a long (q) arm. Chromosomes can't be seen with the naked eye, but they can be stained so that each has a distinctive pattern of light and dark bands when viewed at about 1000 times life-size under a light microscope. You can see these bands for chromosome 15 in the diagram on the next page.

Chromosome 15



Bands are numbered outwards starting from the point where the short and long arms meet (the centromere) (marked in yellow). Chromosome 15 is an example of an acrocentric chromosome, meaning the centromere is located very close to one end, so the p arm is very short. A low band number such as q12 is close to the centromere; this part of the arm that is fairly close to the centromere is called the proximal part. A higher number such as q25 is closer to the end of the chromosome, in the part referred to as distal. The term cen is used to indicate a location that is very close to the centromere, while ter (for terminal) indicates a location that is very close to the end of the p or q arm. Some bands are further divided in to sub-bands e.g. band 15q15 has three sub-bands: 15q15.1, 15q15.2 and 15q15.3.

This guide covers deletions involving bands 15q15 to 15q22 (marked in red). Affected individuals have one unaffected chromosome 15 but their other chromosome 15 has chromosomal material missing from one or more bands between 15q15 and 15q22 on the long (q) arm. Some people have larger deletions that may include multiple bands; others have tiny deletions that include only part of one subband (*see* page 7 for deletions affecting *Unique* members).

Sources

The information in this booklet is drawn from published medical literature and information from *Unique* members. The first-named author and publication date for articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed (http://www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain most articles from *Unique*. Information gathered from DECIPHER (DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources) is open access and can be found at https://decipher.sanger.ac.uk. Six *Unique* members completed a detailed survey in 2021. In addition, information has also been drawn from the database records of other members where possible.

Chromosomal changes

At fertilisation, a sperm cell and egg cell join to form a single cell. This cell must continuously make copies of itself and all its genetic material (replicate) in order to produce the billions of cells that are necessary for human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated replication process, parts of a chromosome(s) are lost, duplicated and/or become rearranged.

The effect of any chromosomal change varies according to how much genetic material is involved and, more specifically, which genes and/or regions that control genes are included, as well as numerous other factors that we are only just beginning to understand.

Genetic tests

With any deletion the amount of missing DNA can vary. Deletions that are so small that they are not visible under the microscope using standard techniques are called microdeletions. Many people who have a microdeletion may therefore have previously been told their standard chromosome analysis was 'normal'.

A laboratory technique called FISH (fluorescence *in situ* hybridisation) enables sections of the chromosome to be analysed in more detail and can help detect a deletion. This technique uses fluorescently-labelled pieces of DNA that match the DNA in specific places on a chromosome, so this test would have been offered only if there was a suspected abnormality in a specific region of a chromosome.

The more commonly used test nowadays is called chromosomal microarray (CMA) and allows genomic DNA to be analysed in greater detail. An array test can detect very small microdeletions even when this diagnosis is not suspected. It will also identify a more precise position on the chromosome for the piece of DNA that has been deleted.

Advances in next generation sequencing (NGS) technologies offer the promise of ever-more accurate diagnoses and understanding of rare chromosome disorders. NGS allows multiple genes; the entire protein-coding portion of all the genes in the genome (whole-exome sequencing (WES)); or even the entire genome (whole-genome sequencing (WGS)), rather than just targeted regions or individual genes, to be sequenced. This allows variation across the entire genome to be assessed and may be particularly useful for detecting microdeletions that may be missed by less sensitive microarray analysis.

Mosaicism

NGS technologies can also more accurately diagnose low-level mosaicism. Mosaicism occurs when not all cells in the body have the same numbers or

arrangements of chromosomes and typically arises in the affected individual early in the development of the embryo after fertilisation. Usually, this means that one "population" of cells with a 15q deletion could exist alongside another "population" of cells with a "normal" chromosome number and arrangement. The proportion of cells in the different tissue types that make up the body with each arrangement can vary, which will influence an individual's features.

However, the true degree of mosaicism isn't easy to determine as tissues that may be particularly important to development, such as the brain, cannot be easily investigated, unlike blood cells or cells in the saliva that are usually used for testing. Mosaicism is uncommon, and at the time of writing there appeared to be no reports of an individual with mosaicism involving a 15q deletion in this region, but where it has been reported in medical literature for other rare chromosome conditions, the outcome was in some cases milder.

Chromosome test results

The results of genetic (genomic) testing are likely to be given to you by your geneticist or a genetic counsellor. They will talk you through the results and can also tell you more about the genes and chromosome material that have been deleted. Depending on the test that was carried out, someone with a deletion involving the 15q15 to 15q22 region of chromosome 15 might have results similar to one of these examples:

46,XY,del(15)(q21.1q22.3) This result shows that the expected number of chromosomes (46) were observed. It also shows that an X and a Y chromosome were found, so this is a boy or a man. del(15) means there is a deletion involving chromosome 15. (q21.1q22.3) shows the part of the chromosome that is deleted; in this case, there are two breakpoints, one in band q21.1 and one in band q22.3. The genetic material between these two points is missing.

arr[hg19] 15q15.3q21.1(44512745_46787207)x1 dn This result shows that the analysis used microarray technology (arr). The analysis revealed a DNA anomaly involving 15q15.3 to 15q21.1. The DNA anomaly is identified by its base pair numbers (the points where the change has occurred). In this example, the DNA anomaly lies between base pairs 44512745 and 46787207 (by taking the first number from the second, you can work out that this is 2,274,462 base pairs, or 2.27 Mb). There is a missing copy (x1; the normal copy number is two), so 2.27 Mb of DNA between base pairs 44512745 and 46787207 have been shown to be deleted. hg19 tells you which version of the human genome was used for comparison (*see* Genome Assemblies (blue box), page 6). The deletion occurred dn or *de novo* (as a 'new event'): the parents' chromosomes have been checked and no deletion or other chromosome change has been found so the deletion has not been inherited from either the father or the mother.

Genome Assemblies

The human genome project, an international effort to sequence the entire human genome and map all of its genes, was announced complete in 2003. However, there were many gaps in the sequence and mapping data, and scientists have since been working continuously to identify the missing information. When new sequence information is identified, the base pair numbers of each chromosome change slightly and hence the numbers for individual genes and deletions can shift.

Each new version of the genome is often referred to as an 'assembly'. Every few years a new assembly is released. The genetic information you are given will be based on the Genome Reference Consortium (GRC) human (h) genome assembly that was the most up-to-date at the time the test was carried out. Therefore, you may see the DNA sequence referred to as hg19 (human genome 19) (on your child's genetic report it may also be referred to as GRCh37), which was released in 2009, or hg 18, which was released in 2006. The lower the hg number, the earlier the release.

At the time of writing, the databases commonly used by clinical geneticists and *Unique* were moving to a more recent assembly named GRCh38/hg38, which was released in 2013. Genetic reports are also now using coordinates based on the GRCh38 assembly and it is important to remember that genes and genetic changes may have new locations and base pair numbers depending on the assembly used.

arr[hg38] 15q21.3 (53981810_54265166)x1 pat This result shows that the analysis used microarray technology (arr). The analysis revealed a DNA anomaly involving 15q21.3. The DNA anomaly is identified by its base pair numbers (the points where the change has occurred). In this example, the DNA anomaly lies between base pairs 53981810 and 54265166 (by taking the first number from the second, you can work out that this is 283,356 base pairs, or 0.28 Mb). There is a missing copy (x1; the normal copy number is two), so 0.28 Mb of DNA between base pairs 53981810 and 54265166 have been deleted. hg38 tells you which version of the human genome was used for comparison (*see* Genome Assemblies). The deletion has been inherited from the father (pat).

You may wish to compare your child's genetic test results with others - both in medical literature and within *Unique* - who have the same or a similar deletion or microdeletion, to help understand your child's development. While this may help identify common consequences, it is important to remember that the same deletion can have different effects on different people. A person's other genes, environment and unique personality also help to determine their future development, needs and achievements. It is very important to see your child as an individual and not to rely on direct comparisons with others who appear to have the same or a similar deleted piece of DNA. After all, each of us is unique.

How common are deletions involving 15q15 to 15q22?

It is important to note that the information we have relating to these deletions is very limited and therefore provisional. This makes it difficult to estimate the prevalence of deletions involving this region alone; many affected people will not have been diagnosed, and many of those who are diagnosed are not reported.

While there is evidence that there are "critical regions" in 15q15 to 15q22 which if deleted are associated with certain features (*see* Common Features, pages 10-12), some of the deletions we know about are so-called "variants of uncertain (or unknown) significance" (VUS or VOUS). This means it is unclear whether they are causal of the features mentioned later in this guide or if there is another cause, such as another as-yet undiagnosed genomic variant. These 15q deletion VUS may be reclassified as either benign (they have no ill effect) or pathogenic (causative of the observed features), as we learn more about them. The majority of deletions we do know about seem to be microdeletions, with far fewer cases of larger deletions (Fryns 1982; Yip 1986; Fukushima 1990; Martin 1990; Koivisto 1999; Shur 2003; Liehr 2003; Hutchinson 2003; Pramparo 2005; Lalani 2006; Hiraki 2008; Tempesta 2008; Knijnenburg 2009; Faivre 2010; Hilhorst-Hofstee 2011; Abdelhedi 2012; Yamamoto 2014; Jaiswal 2014; Velázquez-Wong 2015; Dordoni 2017; DECIPHER; Unique).

When this guide was compiled, *Unique* had 39 member families with a deletion involving this region alone. These breakpoints are recorded for members of *Unique* (bracketed numbers indicate the number of affected members):

15q15.1q15.1 (1)	15q21.1q22.1 (1)	15q22.1q22.3 (1)	15q23q23 (1)
15q15.1q21.1 (3)	15q21.1q22.3 (1)	15q22.1q23 (1)	
15q15.2q21.1 (1)	15q21.2q21.2 (2)	15q22q22 (1)	
15q15.2q21.2 (2)	15q21.2q21.3 (2)	15q22.31q22.31 (2)	
15q15.2q21.3 (2)	15q21.2q22.1 (1)	15q22.2q22.2 (2)	
15q15.2q22.1 (1)	15q21.2q22.2 (1)		
15q15.3q15.3 (3)	15q21.3 q21.3 (1)		
15q15.3q21.1 (1)	15q21.3q22.2 (4)		
15q15.3q21.2 (1)	15q21.3q22.31 (3)		

Note: As with some cases in medical literature, some *Unique* members have a 15q deletion alongside another chromosomal anomaly(ies). This guide was compiled using data only relating to individuals with a 15q deletion involving the 15q15 to 15q22 region alone and no other known chromosomal anomaly since, for others, the reason for their features may be due to the other chromosomal change(s). This guide may nonetheless be of help to explain any observed features. *Unique* also has further guides to 15q deletions that may be useful to members with larger deletions or deletions involving other regions.

Why did this happen?

To answer this question, both the parents' and the affected child(ren)'s chromosomes need to be tested. What is certain is that, as a father or mother, there is nothing you did to cause the deletion and nothing you could have done which would have prevented it. Chromosome rearrangements affect children from all parts of the world and from all types of background. They also happen naturally in plants and animals. It is no one's fault.

Deletions in the 15q15 to 15q22 region are known to occur *de novo* (dn), which means the deletion has occurred as a new event in the child, or they may be inherited from a parent. While for many the origin of the deletion is unknown, the majority of deletions where the origin is known appear to have arisen *de novo*.

Regardless of the origin of the deletion, as stated above, it is important to know that as a parent there is nothing you could have done to prevent the deletion from happening. No environmental, dietary or lifestyle factors are known to cause 15q deletions. There is nothing that either parent did before, during or after pregnancy that caused the deletion.

Can it happen again?

The possibility that a couple will have another pregnancy affected by a 15q deletion depends on their chromosomes. Where both parents are determined to have unaffected chromosomes, it is very unlikely that another child will be born with a 15q deletion or any other chromosome disorder. Rarely, both parents have unaffected chromosomes by a blood test, but some of their egg or sperm cells carry a chromosomal change. This is called germline (gonadal) 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 15q deletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 15q deletion theoretically rises to 50% (1 in 2) in each pregnancy. However, the effect of the deletion on that child's development, health and behaviour cannot be reliably predicted.

If your child with a 15q deletion goes on to have children of their own, the chances of passing on the deletion to their child are also theoretically 50% (1 in 2) in each pregnancy. Your child's ability to look after their own child is very likely to be closely related to their own learning ability and behaviour.

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

Are there people with a deletion in this region who are unaffected by the deletion?

The DECIPHER database (*see* page 38) lists a few cases of tiny microdeletions inherited from a seemingly unaffected parent. For many of the entries in DECIPHER where a deletion involving the 15q15 to 15q22 region is reported, the significance and/or contribution of the deletion to any observed feature is also listed as unknown or uncertain.

Diagnosis

The age of diagnosis among *Unique* members varied considerably. While roughly half received a diagnosis at or soon after birth, others underwent genetic testing during childhood - between one and 9 years - usually as the result of a delay in reaching developmental milestones or health concerns.

"Diagnosed at five years. Her teacher was concerned due to mild learning difficulties, a tendency to regress after learning a concept and anxiety. They could see differences between her and the other children. The neurologist could tell from her facial features." - del 15q21.2q21.3

Common Features

Deletions involving this region of chromosome 15 can be divided broadly into larger deletions spanning several bands e.g. 15q15 to 15q21 or q22, and smaller deletions involving only part of an individual band or sub-band.

When a particular set of features occurs as a result of a single cause, in a recognisable and consistent pattern, and in enough people, the condition is called a syndrome. While data is limited, attempts have been made to identify features that are consistently associated with deletions involving particular bands or subbands in this region.

Although small in number, these studies led to the identification of a novel 15q21 deletion syndrome affecting those with deletions that include a 2.8Mb critical region in 15q21.1q21.2. They also pointed towards a critical region in 15q22.2 that when deleted is associated with neurological symptoms, including intellectual disability and seizures. Further, they suggested that if the *FBN1* gene located in 15q21.1 is deleted, features that are characteristic of Marfan Syndrome (MFS) may be observed (*see* page 11 & Genes).

It is important to remember that just as typically-developing children can

experience a number of unforeseen physical and behavioural concerns, each person with a 15q deletion involving this region is unique and the developmental and medical concerns they experience vary from person to person. It is also important to bear in mind that when assessing people, doctors usually focus on areas of difficulty rather than strength or normality. Nevertheless, the most common features associated with 15q deletions in this region, and/or those that are the most likely to make a difference to a child's health or development if they experience them, are outlined below.

Most common features of people with deletions spanning 15q15-q22:

- Some degree of developmental delay
- Some degree of cognitive impairment, ranging from mild learning difficulty to intellectual disability
- Delayed/absent speech
- Growth retardation (babies are small/light for their age)
- Floppiness or low muscle tone (hypotonia)
- Feeding difficulties in the new-born period
- Characteristic facial features, including: an unusually-shaped nose which is often prominent with under-developed nostrils; a thin upper lip; low set-ears; a high/arched roof of the mouth (palate)
- Anomalies of the eyes/concerns with vision

Less common features include:

- A heart condition
- Cryptorchidism (undescended testes)
- Anomalies affecting the skeleton - including an unusual head shape e.g. craniosynostosis
- A brain anomaly

(Fukushima 1990; Koivisto 1999; Shur 2003; Hutchison 2003; Hiraki 2008; Abdelhedi 2012; DECIPHER; Unique)

Features of deletions including the critical region for 15q21 deletion syndrome:

- Characteristic facial features, including: a beak-like nose with under-developed nostrils and a thin upper lip
- Some degree of developmental delay
- Some degree of cognitive impairment, ranging from mild learning difficulty to intellectual disability

- Delayed speech
- Growth retardation (babies are small/light for their age)

Possible additional features depending on the size of the deletion include:

- Floppiness or low muscle tone (hypotonia)
- Microcephaly (an unusually small head)
- Craniosynostosis (an unusually shaped head)
- Brain anomalies
- Unusual features of the hands and feet, including small hands and feet
- Genital anomalies
- Late-onset truncal obesity
- Diminished fetal movements during pregnancy
- Additional facial features

(Fryns 1982; Yip 1987; Martin 1990; Liehr 2003; Pramparo 2005; Lalani 2006; Tempesta 2008; Yamamoto 2014; Velázquez-Wong 2015; DECIPHER; Unique)

Features of deletions involving the 15q22.2 critical region:

- Some degree of developmental delay
- Some degree of cognitive impairment, ranging from mild learning difficulty to intellectual disability
- Seizures/epilepsy
- A squint (strabismus)
- Brain anomalies
- Characteristic facial features, including: a square-shaped face with a prominent forehead; a shorter than normal philtrum (the distance between the upper lip and nose); thin lips and a pointed chin

(Yamamoto 2014; Velázquez-Wong 2015; DECIPHER; Unique)

Features of deletions that include the *FBN1* gene:

Marfan Syndrome (MFS) is a genetic condition that affects approximately 1 in 5,000 to 1 in 10,000 people. The vast majority of cases are caused by a change (variants) in the *FBN1* gene, which is located in 15q21.1 (*see* Genes, page 35). MFS affects many different parts of the body but is especially associated with problems with the heart, blood vessels, joints, bones and eyes. People with MFS are also usually tall and slender. MFS is not associated with intellectual disability.

The combination of features that an individual with MFS experiences varies from person to person, as does the age at which symptoms first appear.

Some features may only emerge later in life, while others can appear at any age. It is also important to remember that the degree to which an individual will be affected varies considerably.

When a 15q deletion includes the *FBN1* gene, additional features associated with MFS may also be observed over and above those classically associated with other 15q deletions.

Possible additional conditions associated with FBN1 gene deletions:

- Problems with the heart and blood vessels (mostly problems with valves within the heart or aortic artery enlargement)
- Curvature of the spine (scoliosis or kyphosis)
- Over-flexible joints (joint hypermobility)
- A chest the sinks in (pes Pectus excavatum) or sticks out (pectus carinatum (pigeon chest))
- A tall and thin body type
- Unusually long arms, legs and fingers
- Wasting of the limbs and muscle weakness
- Stretch marks on the skin that are not associated with gaining or losing weight
- Problems with vision/structural eye anomalies
- Crowded teeth

(Koivisto 1999; Shur 2003; Hutchinson 2003; Pramparo 2005; Ades 2006; *Lalani 2006?;* Singh 2007; Hiraki 2008; Faivre 2010; Hilhorst-Hofstee 2011; Colovati 2012; Dordoni 2017; DECIPHER; Unique; Marfan Trust (www.marfantrust.org); The Marfan Foundation (www.marfan.org))

Pregnancy

The limited information we have suggests that while some pregnancies are uncomplicated with no concerns reported, in other cases there may be some grounds for concern during pregnancy. Typically, there may be too much (polyhydramnios) or too little (oligohydramnios) amniotic fluid around the baby. In other cases, the baby may be noted to be growing slowly (intrauterine growth retardation) or sometimes moving too little (diminished fetal movements). In one case in medical literature, scans revealed an unusually short thigh bone measurement and two *Unique* members told us that a routine scan revealed an increase in the nuchal translucency thickness (Fryns 1982; Yip 1987; Fukushima 1990; Martin 1990; Koivisto 1999; Liehr 2003; Shur 2003; Pramparo 2005; Tempesta 2008; Abdelhedi 2012; Yamamoto 2014; Dordoni 2017; DECIPHER; Unique).

Birth & new-born babies

3 months

While some babies have a routine delivery and post-natal period, a significant number can be expected to experience some degree of difficulty in the new-born period.

Babies are sometimes light for dates at birth, but this trend is not universal and some have an average or above-average birth weight. From the limited data available, it appears that head circumference (HC) measurements at birth are often below average.

Babies are sometimes floppy (hypotonic) and they may have difficulty establishing feeding. Some may have difficulty establishing breathing or stop breathing for a spell (apnoeas) in the newborn period, requiring extra oxygen either short or longer term. A few babies have had neonatal jaundice (Fukushima 1990; Martin 1990; Koivisto 1999; Shur 2003; Pramparo 2005; Lalani 2006; Hiraki 2008; Tempesta 2008; Abdelhedi 2012; Yamamoto 2014; DECIPHER; Unique).

“ Induced at 38 weeks and weighed 7lbs 12oz (3.52kg). No concerns in the new-born period. Did have reflux, which didn't persist in to childhood ” - del 15q21.3, 5 years

“ Thickened nuchal translucency at 12 week scan. Delivered by C-section at 38 weeks because baby was lying transversely. Baby had respiratory distress at birth due to hyaline membrane disease [also known as infant respiratory distress syndrome or surfactant deficiency lung disease. This condition occurs almost exclusively in premature infants]. Spent five days in NICU and three weeks in neonatology unit. ” - del 15q15.2q21.3, 11 years

“ Born at 41 weeks. Weighed 8lb 12oz (3.99kg) and was 53 cm long. No concerns in the new-born period. ” - del 5q21.3q22.2, 9 years

“ Had to stay one night in hospital due to reduced fetal movements. Born at 38 weeks, weighing 6lb 4oz (2.85kg). She had an umbilical hernia but it closed [spontaneously] six to seven months after her birth. ” - del 15q21.3q22.2, 3 years

Growth

It appears that some children maintain an average weight and height compared to the general population throughout baby- and childhood. For others, after an initial growth delay so the child is short for their age, there is then rapid weight gain - even in babyhood - around the abdomen so that they are relatively plump for their height. This pattern of relative plumpness

(truncal obesity) - sometimes associated with 15q21 deletion syndrome - has been seen in adults, even when they have shown catch-up growth and achieved a "normal" adult height. Several *Unique* members are described as extremely short for their age: one was as tall as a three-year-old at nine years; another 10-year-old was taking growth hormone to boost his height.

1 year

Medical literature suggests that children with a deletion including the *FBN1* gene may have the tall, thin body-type seen in children with MFS, but this is inconsistent and appears to be more associated with smaller deletions in the 15q21.1 region (Ades 2006; Hilhorst-Hofstee 2011; Colovati 2012; Faivre 2012; Dordoni 2017; DECIPHER, Unique).

"Average height and above average weight (4 ft and 136lbs). Short and stocky build." - del 15q15.1q21.1, 10 years

"No growth delay. Average height and weight. He's very solid." - del 15q21.3, 5 years

"She is smaller than average, mostly in weight, but also a little in height." - del 15q21.3q22.31, 8 years

"Average height and weight. He is not that tall but he is quite slender (no fat)." - del 15q21.3q22.2, 9 years

"No growth delay. Has some weigh concerns, does tend to over eat and craves sugar. Average height and mildly overweight." - del 15q21.2q21.3, 11 years

Feeding

Feeding difficulties, especially in the new-born period, are common among babies with a rare chromosome disorder. The evidence from *Unique* and medical literature is that babies generally need considerable support to establish effective feeding. While some babies have seemingly fed well - one child is described with an "immense appetite" - most babies have fed slowly and been unable to cope with breastfeeding, but managed better with a bottle.

Some babies have gastro-oesophageal reflux (GORD, GERD), where feeds frequently and forcefully return up the food pipe from the stomach. There are many simple measures that may help to control reflux, including positioning semi-upright for feeds and using a cot with a raised head end; your doctor can prescribe feed thickeners and medication to help feeds stay down and counteract any effect of acidity on the food pipe. Where feeding and reflux problems are persistent, a nasogastric (NG) tube or gastrostomy tube

(PEG, button), to allow direct feeding into the stomach, may be needed. While some babies are described as having more severe feeding difficulties, with persistence these problems have resolved, generally without the need for long-term tube feeding.

Constipation was mentioned by several *Unique* families. Where there are concerns, it is important that parents discuss the possible causes with their health visitor or doctor, who may recommend adapting a child's diet or giving stool softeners such as Movicol or laxatives such as Lactulose and Senna.

Several families mentioned that their child had an intolerance or allergy to certain foods and some were "fussy" eaters.

Where we have information, babies known to *Unique* have often made slow but steady progress with feeding. Progress to solids has also been delayed and children have spent longer than usual taking pureed or mashed foods before learning to tolerate lumps.

For babies with early feeding difficulties, feeding times can become stressful and some children who have overcome their difficulties with swallowing, reflux or chewing nonetheless become food-averse. Ask your GP, health visitor, speech therapist or paediatrician about specialist feeding clinics to help with the 'can eat, won't eat' scenario that can then develop (Martin 1990; Lelani 2006; Hiraki 2008; Le Tanno 2014; Unique).

❝ Couldn't drink liquids and we had to thicken everything. In the new-born period he had severe feeding problems with constipation and reflux. Problems didn't extend into childhood. He has seen a feeding therapist. ❞ - del 15q15.1q21.1, 10 years

❝ Coughed when feeding. Lost weight in the first week but then gained weight well. Breast fed but had very weak neck muscles and dribbled a lot. ❞ - del 15q21.2q21.3, 11 years

❝ Breast fed. No major concerns now but he often complains of pain in the tummy and has an explosive and loose bowel movement fairly regularly. ❞ - del 15q21.3q22.2, 9 years

❝ My new-born daughter lost a little more than 12% of her birth weight due to feeding difficulties. On doctor's suggestion we switched to formula to make sure we knew how much she was feeding and slowly she started gaining weight. ❞ - del 15q21.3q22.2, 3 years

.❝ Experienced severe constipation from about three months but not as often now. She took a magnesium supplement once daily for several years, but is now normal without any supplements. She has trouble occasionally, but is mostly regular. ❞ - del 15q21.3q22.31, 8 years

Appearance

Children with a 15q deletion in this region sometimes have facial features in common. Typically, babies may have under-developed, flat nostrils leading to a beak-shaped nose; a broad nasal bridge; ears set below the line of the eyes, sometimes large or unusually shaped; a short neck; a small or receding lower jaw and chin or, conversely, a protruding jaw; a small mouth, sometimes held open, with a thin upper lip; arched eyebrows; a short neck; a high, arched roof of the mouth (palate); and unusual skin (which may be notably pale and dry), eye and hair colour compared with the rest of the family. A few families mentioned that their child has fine or sparse hair.

While many of these characteristic features are common to those with both large and small 15q deletions in this region, evidence suggests that a beak-shaped nose is only seen in those with deletions that include the 2.8Mb critical region in 15q21.1q21.2 that leads to 15q21 deletion syndrome and is not observed in children with 15q deletions not including this region (Martin 1990; Liehr 2003; Pramparo 2005; Lalani 2006; Hiraki 2008; Tempesta 2008; Knijnenburg 2009; Papadopoulou 2010; Hilhorst-Hofstee 2011; Abdelhedi 2012; Le Tanno 2014; Yamamoto 2014; DECIPHER; Unique).

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

For babies and children with a deletion between 15q15 and 15q22, whether large or small, a delay in reaching motor milestones is to be expected. The extent of the delay can be very varied, ranging from mild to severe, and will affect the amount of support a child needs. There may be several reasons for these delays, including reduced muscle tone (hypotonia) and decreased strength, which can make achieving mobility milestones more difficult, although muscle tone often improves with age. Especially in children with deletions encompassing the *FBN1* gene, joint hypermobility may also make motor milestones harder to achieve. *Unique* parents also mentioned concerns around co-ordination and balance.

A similar picture was seen among *Unique* members and in medical literature. Most children we know about started to walk between 18 months and 3 years. In medical literature, a boy with a 15q21.2q22.1 deletion showed moderate developmental delay; while he was not crawling at 12 months, by 2 years 3 months he was walking with support and was fully mobile by 3 years 9 months. A four-year-old boy with a 15q21.1q22.2 deletion walked independently at 16 months, but at four years of age was not yet capable of walking down stairs. Two children with 15q21.3q22.2 deletions exhibited a motor delay from early infancy, but started to walk between 24 and 31 months. Individual children with a deletion including the *FBN1* gene have demonstrated global motor delay but were walking

independently by 16 and 18 months. Loose joints, which are particularly associated with deletions involving the *FBN1* gene, can lead to some clumsiness and may mean that children need supportive footwear or splints, especially for the ankles, in the early stages of walking (Martin 1990; Lalani 2006; Colovati 2012; Yamamoto 2014; Dordoni 2017).

Regular physiotherapy (PT) can be beneficial in helping improve motor skills and physical development, including co-ordination, balance and mobility. The use of orthotics if needed, such as support boots, may also help increase mobility.

“ He has moderate developmental delay. He’s now on a kindergarten level at 10 years. ” - del 15q15.1q21.1, 10 years

“ She is very mildly affected. She is extremely enthusiastic and works hard to overcome any disadvantages. She crawled at 17 months and walked at 18 months. Very delayed in rolling and sitting. ” - del 15q21.2q21.3

“ He has moderate or severe developmental delay - he has been slow to develop in most areas and was late reaching most of the usual milestones: sitting, crawling, feeding himself, speaking, walking. He rolled at 12 weeks, sat at 4 months, but would fall over easily, and walked at 26 months. We saw a podiatrist when he was 2 years old who said that he has hyper-mobility in his joints, which caused him to feel very unsteady when walking. She made inserts for his shoes (shoes with a high top to support his ankles) that helped to support his hips and ankles. Soon after wearing these he became a lot more confident and started walking independently. ” - del 15q21.3q22.2, 9 years

“ She was late in achieving all her milestones during the first two years. She started crawling when she was 10 months old and started walking only around 22 months and is still a bit wobbly on uneven surfaces. She seemed to lack confidence and needed lot of hand holding. She is three years old now and is one year behind. ” - 15q21.3q22.2, 3 years

Development: hand use and coordination (fine motor skills) & self-care

Hand-eye coordination skills, such as holding a bottle and playing with small

toys, may not develop in line with gross motor skills. Information relating specifically to these fine motor skills is scant, but from what we know from *Unique* families there appears to be a fairly consistent delay. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. In medical literature, a four-year-old with a 15q21.1q22.2 deletion who was able to throw and catch a ball and use a spoon was assessed as functioning at the level of a 25-26 month-old with mild to moderate delay. Early intervention by occupational therapy (OT) to stimulate hand use is usually very beneficial, while jigsaws, Lego, dot-to-dot pictures, peg boards and shape-sorters can all be helpful in encouraging these skills to develop (Lalani 2006; Unique).

Toilet training is also likely to be delayed but the degree of delay is very varied: one *Unique* child was toilet trained by four years; three children at around five years; and two children at around 7 years.

“ He has trouble with zips and can’t tie shoe laces but can trace okay lately. He was toilet trained at ABA (Applied Behaviour Analysis) therapy at the age of five. ” - del 15q15.1q21.1, 10 years

“ She has difficulties with fine motor skills, including things like doing up buttons and her school tie. OT has helped a lot. ” - del 15q21.2q21.3, 11 years

“ Toilet trained at five years. He’s been out of nappies in the day since he turned five but is still in them at night. ” - del 15q21.3, 5 years

“ He was delayed in his ability to use cutlery, wipe his bottom, write/draw and play with toys but he has shown slow and gradual improvement as he gets older. He was toilet trained during the day at three years six months and overnight at four years. ” - del 15q21.3q22.2, 9 years

Ability to learn

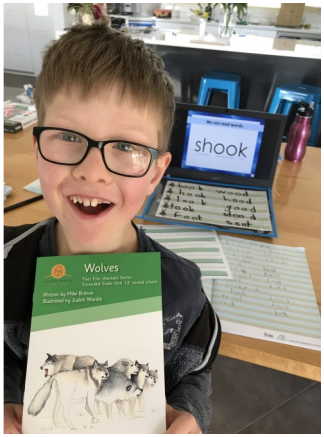
Learning difficulties and learning (intellectual) disability are common in children with a 15q deletion in this region, ranging from mild to profound. Although it is not possible to precisely predict the degree to which a child will be affected by their individual deletion, there is some evidence that those with larger deletions are likely to be more significantly affected (Lalani 2006; Martin 1990; Pramparo 2005; Tempesta 2008; Faivre 2010; Hilhorst-Hofstee 2011; Colovati 2012; Yamamoto 2014; Dordoni 2017; DECIPHER; Unique).

Most children will need support with their learning to achieve their full potential. Placement in regular (mainstream) or special school may depend as much on local provision as on a child’s abilities. Many *Unique* children have attended a mainstream (public) school, usually within a supported unit or with 1:1 help or dedicated support workers for specific areas of concern. For a child with a more severe learning disability, a school specifically for children with special educational needs may be better equipped to meet their

needs. Where you have concerns, early intervention is important and if your child is diagnosed early enough they may benefit from early intervention programmes.

In the UK, a tailored education, health and care (EHC) plan can be issued after a child has undergone an EHC needs assessment. This legally-binding document ensures that the educational, health and social provisions deemed necessary to support a child's needs are delivered.

For further information, *Unique* has a dedicated guide to "Education" in the practical guides for families section of our website.



"He has moderate intellectual [learning] disability. He attends a public [mainstream] school and is in a class of four children with two adults. He is learning at his own pace using the unique program." - del 15q15.1q21.1, 10 years, US

"She is in a mainstream school and has always scored low average in tests. She works very hard, however, and has had a lot of support from parents and therapy. She would appear at times to regress and then do really well other years. Now, in Year 6, she has really caught up and is excelling. She still struggles with verbal comprehension at times. She is on a CAP but she has now caught up with reading and writing so it is now more in use for her tiredness and anxiety." - del 15q21.2q21.3, 11 years, Australia

"He attends a mainstream primary school with an EHCP. I found the process of obtaining it took a long time." - del 15q21.3, 5 years, UK

"It takes him a long time to acquire new skills and if he is not interested in a task he is reluctant to try very hard. He is not at level for any specific area but he likes to read and he likes to use technology. He had an assessment with the diagnosis of intellectual disability that gave him funding for an aide in mainstream school. It has been great for him to receive support and he would be unable to attend without it. He is very sociable and loves interacting with the other students. I'm not sure if his learning ability has changed. It seems to be slow but steady progress. It is encouraging that he continues to develop slowly but surely but we are unsure what his eventual level of independence will be. Eventually he will go to a special needs school but at the moment he is doing well and is happy." - del 15q21.3q22.2, 9 years, Australia

"She goes to mainstream nursery three days a week and just started going to a special needs nursery two days a week. She has no diagnosis yet but she

takes more time than her peers to learn anything new and she finds it difficult to acquire new skills. We are planning to apply for an EHCP this year and are currently doing research on what kind of school is best suited for her needs." - 15q21.3q22.2, 3 years, UK

"She loves learning, but struggles a lot. She learned colours and names of people early on and learns well with music. She remembers dance steps easily. She is always progressing! She attends a regular public [mainstream] school which provides therapies and a special education classroom and Individualized Education Program (IEP). We have annual meetings and can meet any other time we request." - 15q21.3q22.31, 8 years, USA

Speech and Communication

The limited information we have suggests that speech and language is typically one of the most commonly affected areas of development and is sometimes severely affected; for others the delay is more mild.

Unique parents often felt that their child's comprehension (receptive language) was significantly better than their ability to communicate using language (expressive language), but this was not the case for all. Many parents also mentioned that their child has articulation difficulties, making it difficult to make clearly intelligible speech. Where speech did develop, with time some parents of older children told us they had gone on to make significant progress and use long, complex sentences.

From medical literature, we know that a four-year-old boy with a 15q21.1q22.2 deletion and moderate speech delay was able to name body parts, speak in simple phrases and follow simple commands. He benefited from receiving speech therapy to help with his speech/language delay. One child with a 15q21.3q22.2 deletion spoke her first meaningful words at 11 months and by the age of three was able to understand simple instructions and could form some words such as "sweet" and "dangerous", but was limited to two-word phrases. A 13-year-old boy with a 15q22.2 deletion spoke his first meaningful words at 3 years.

There are many reasons for a speech delay, including the link between the ability to learn and the ability to speak. Hypotonia can result in weakness in the mouth muscles which can affect the development of speech. Where individuals have no speech or very few words, communication may be enhanced through augmentative/alternative communication (AAC) e.g. Makaton, signing, gesture, facial expression, Picture Exchange Communication System (PECS) and iPad communication. AAC has proved beneficial for many *Unique* children, especially in the early years, and can also help reduce the impact of any frustration that a child may feel as a result of not being able to communicate their needs and wants effectively.

An assessment by a speech therapist should be able to identify if your child

has a specific difficulty. Where regular therapy sessions are advised, they should be tailored to your child's specific areas of need. Speech therapy has helped many *Unique* members, including those with 15q deletions. Any concerns around hearing should also be acted on early to help reduce any impact on speech (Martin 1990; Lalani 2006; Yamamoto 2014; Dordoni 2017; DECIPHER; Unique).

"He was non-verbal until about five years. He advances really well for a while then levels off for a few months. He finds it difficult to make sounds of speech clearly and still can't have a conversation with you but we understand his needs and wants." - del 15q15.1q21.1, 10 years

"Speech was delayed and we didn't find out about glue ear until five years of age so are unsure how much was due to hearing issues. With speech therapy, which has been on-going since five years, it is now all corrected. At 11 years, she now uses complex sentences but she still isn't quite on the same level as others her age. Had a lisp which is now gone." - del 15q21.2q21.3, 11 years

"He started to speak at five years and his speech is severely delayed. He finds it difficult to make the sounds of speech and not many people can understand him. He uses sentences such as: "Mummy can we go outside?" . His ability to express himself is better but he doesn't always understand. He uses PECS and Makaton and he has been referred for an iPad communication app through his speech therapist." - del 15q21.3, 5 years

"Until three years, he didn't talk but would communicate with some key word signs like: more, food, finished, banana, book and Wiggles! He seemed to understand some simple instructions like: "Give this to dad." or "Where are your shoes?". His lack of communication was his biggest difficulty.

He spoke his first word at around three years. He continued to use key word signs and gradually added more words. Age 9, he can speak in four- to seven -word sentences (which are not always grammatically correct). He can understand most things and is pretty good at expressing what he wants, but at times it is hard to understand what he is trying to say due to the clarity of his speech sounds and because he misses some words. This may be due to low muscle tone in his mouth/tongue.

We have found speech therapy to be very helpful in enabling our son to communicate with us. We still continue to have regular sessions and his speech continues to improve." - del 15q21.3q22.2, 9 years

"She has speech delay. She can speak two to three words but does make lots of sounds. We have started speech therapy for her and use PECS and Makaton to help her communicate with us, but most of the time if she needs anything she will point to the object or hold my hand and take me to the object if it's not in the same room. She is making progress but it is slow. She

Types of social, emotional and anxiety disorders

Attention Deficit Hyperactivity Disorder (ADHD): ADHD is usually diagnosed between the ages of six and 12 years. The disorder is characterised by a range of behaviours, including hyperactivity, inattentiveness and impulsiveness that make it difficult for children to concentrate and control their actions and speech. Children are often described as "restless", are easily distracted and may talk or interrupt a lot.

Autism Spectrum Disorders (ASD): ASDs include autism and are associated with impaired social skills; problems with communicating; and a need to carry out restricted repetitive and restrictive behaviours, interests and activities, from which an individual derives comfort.

Obsessive Compulsive Disorder (OCD): A related but distinct disorder, which may co-exist alongside an ASD or manifest separately, those with OCD experience anxiety that can be relieved to some degree by carrying out specific, repetitive rituals e.g. obsessive hand-washing, repetitive counting/ checking. Those with OCD don't derive pleasure from these routine behaviours, but fear that something bad will happen if they don't complete them.

Sensory Processing Disorder (SPD): A child with SPD finds it difficult to process and act upon information received from the world around them through their senses e.g. sound, touch. This makes carrying out everyday tasks and responding to different environments challenging. Typical features of SPD include heightened reactions to sound, movement and touch; clumsiness; behavioural and social problems; difficulties with concentration; and disrupted sleep patterns.

Oppositional Defiance Disorder (ODD): A child with ODD becomes annoyed easily and is liable to frequent temper tantrums. They will also challenge authority, refusing to obey rules. This behaviour can appear to be deliberate and can present problems with social interactions.

finds it difficult to make the sounds of speech clearly. She understands a lot of things but due to her speech delay she can't express herself as clearly as she would like to. She has had speech therapy on a weekly basis since she was two-and-a-half years old. ” - del 15q21.3q22.2, 3 years

“ She uses a lot of mostly simple language and does not always speak in full sentences but uses simple, short sentences with a limited vocabulary and talks a lot in the third person. She often repeats words or phrases. She finds it difficult to make the sounds of speech clearly and definitely understands much more than she can say. ” - del 15q21.3q22.31, 8 years

Personality & Behaviour

The testimony we have from *Unique* families speaks to children who are happy, sociable, loving and affectionate individuals. In common with their peers, children enjoy being outdoors and relish a range of activities.

A significant number of children – although not all – show a similar pattern of behavioural difficulties. There appears to be a tendency for children to find social interactions challenging. This is often exacerbated by difficulties with speech that can lead to frustrations and misunderstandings when communicating with others. Some children display inappropriate levels of friendliness and need to be monitored closely.

A diagnosis with one or more social, emotional or anxiety disorder, including ASD, ADHD and SPD, was reported by a number of *Unique* families. Some children had shown features of these disorders but had not received an official diagnosis (*see* testimonies below and Types of social, emotional and anxiety disorders, page 22). Where we have information from medical literature a similar pattern was seen, including one child with a microdeletion involving 15q22.2 who exhibited some self-injurious behaviour, such as head banging when she was told off, and a girl with a small 15q21.1 deletion including the *FBN1* gene who displayed behaviour that was described as “hyperactive”. At the age of five years, a boy with a 15q21.2q22.1 deletion found it difficult to control his emotions, crying more frequently than would be expected and sometimes becoming aggressive (Martin 1990; Colovati 2012; Yamamoto 2014; DECIPHER).

Where a parent believes that their child may have a specific disorder - such

as an ASD or ADHD - they should consult their general practitioner/ paediatrician who can refer them to a behavioural or clinical psychologist to undergo assessment. There is not a 'medical test' that can diagnose ASD, but children undergo an autism-specific behavioural evaluation, usually carried out by a specially trained physician and psychologist. The evaluation may be multidisciplinary and include a speech and language therapist as well as an occupational therapist. It is also tailored to the age of the child. Depending on the outcome, further evaluation by a specialist, such as a developmental paediatrician, neurologist, psychiatrist or psychologist, may be offered.

An occupational therapist may be able to help with some behavioural issues by giving your child tools to deal with their sensitivities, if need be. Joining a social skills group may help a child with social difficulties to learn and practise important social skills. A parenting course for autism may also help parents to learn behaviour management skills, and help to encourage communication and cooperative behaviour in their child, to strengthen their emotional wellbeing. Children may be prescribed medication to help with specific disorders following diagnosis - including methylphenidate (Ritalin) for ADHD, which can help with restlessness and inappropriate comments - although this may not be suitable for all.

“ He's very sweet and lovable. He has an ASD. He can be awkward socially and displays challenging and aggressive behaviours. He is now medicated for this. You have to talk to him a certain way or he will get very upset, for instance if he's at a playground and you tell him it's time to leave, but if you set timers then he leaves easily. Most days are good with maybe a couple episodes a day. He loves outside and playing with balls is his favourite activity. He also just learned to ride a bike and loves driving the four wheeler. ” - del 15q15.1q21.1, 10 years

“ She has a very happy disposition and can be very excitable and enthusiastic. She is an extrovert. She is also very trusting, which could be taken advantage of, and is a follower who loves people. She needs a lot of attention and can be loud and silly if comfortable. She loves one on one attention.

She has mild ASD and ADHD traits and high levels of anxiety from a baby to now. Anxiety, socialising and self esteem are the biggest issues we've faced, with temper tantrums even at 11 years. These aren't significant enough for an ASD or ADHD diagnosis but she has been tested. Can become aggressive towards her mum at times, mostly aged 7 to 10, and now at 11 a lot of attitude, but still has a lot of crying episodes to get what she wants. She now has a lot of friends but has had issues in the past. She seems to have embraced her differences and her friends accept who she is. ” - del 15q21.2q21.3, 11 years

“Very happy, cheeky and is always laughing. Can be restless, very hyper and full of energy. Enjoys playing outside and bath time.” - del 15q21.3, 5 years

“We are lucky that our son has had relatively good health and that he is a generally happy and loving boy. He has a beautiful personality and is quite endearing. He can be frightened easily and gets upset. He is fairly easy going but requires constant attention/ reassurance/help.

He is generally good with his siblings. He can demonstrate inappropriate friendliness. He will talk to anyone and loves interacting with others, but they find it difficult to understand him due to his poor pronunciation. He can also be unsure and shy in some situations and was reluctant to leave his mother/father when he was younger.” - del 15q21.3q22.2, 9 years

“She is a very happy and bubbly child, always smiling and giggling. She is kind and loves to share her toys and food with others. She doesn’t demonstrate any challenging behaviours but she does take a while to get adjusted to new surroundings. She is very stubborn and she doesn't like change. She will only drink water from a specific sippy cup or have milk from a specific bottle. As she is still non-verbal she find it difficult to interact with others. She enjoys rhymes, scribbling on papers, colouring, popping bubbles and watching her favourite cartoon. She doesn't like pretend play.” - 15q21.3q22.2 deletion, 3 years

“She is happy, sweet, loving, independent and has always scored well in social skills. She has sensory issues and is sometimes jumpy around certain sounds or visual stimuli. She was assessed for autism but was not diagnosed. Some challenging, defiant behaviour.” - 15q21.3q22.31, 8 years

Sleep

No particular pattern of sleep disturbance has emerged associated with 15q deletions in this region and several parents told us there were no concerns or that their child slept well. A few parents did say that their child had experienced issues around sleep, mainly around restlessness. One child was investigated due to parental concerns and was diagnosed with confusional arousal, in which a sleeping person wakes up - or seems to wake up - but behaves strangely. It was recommended that the parents instigated a later

bedtime, which proved extremely beneficial.

Reasons for sleeping difficulties are not always well understood and are also experienced by many typically-developing children. It can be challenging for all the family when a child does not settle well to sleep or is not getting enough good quality sleep. Our "Sleep problems in children with chromosome disorders" guide, in the practical guides for families section of our website, has further information.

Puberty

The information we have relating to puberty is extremely limited. We do know that for one 14-year-old girl and a 14-year-old boy with a 15q21.3q22.2 microdeletion, no signs of puberty were to be seen. Delayed puberty was also noted for a boy with a 15q21.2q22.1 deletion, although by the age of 18 he had normal, adult male genitalia (Martin 1990; Yamamoto 2014; Unique).

Puberty can be a challenging time for any family. *Unique's* guide to "Puberty" provides helpful information.

Medical concerns

Outlook

The outlook for any child is determined largely by any clinical concerns rather than their genetic diagnosis. Outlined below are some of the most common medical conditions affecting babies and children with a deletion involving the 15q15-q22 region. A significant number of babies in this group spent many weeks or months of their first year of life in hospital, but generally their health later improved significantly.

General well being

Some parents did tell us that their child had been susceptible to colds and other respiratory infections as a baby and in early childhood. A few children have on-going health concerns, including feeding difficulties, anaemia and asthma (Unique). For other *Unique* families, their child's general state of health was not a concern.

"He is generally healthy. When he was younger he had a lot of respiratory infections e.g. colds and chesty coughs. Improved with age and no longer affected."- 15q21.3q22.2, 9 years

Head shape

Babies with a deletion in this region may be born with a head that is an unusual size or shape.

While many babies and children seem to have head circumference measurements that are within the typical range, in some instances the head is unusually small (microcephaly) or large (macrocephaly).

Some babies are born with a large fontanelle (the soft spot on the head of babies due to the space between different plates of a baby's skull that will eventually come together). In some babies, these initially separate bony plates of the skull have fused together too early, causing the head to take on an unusual shape (craniosynostosis). In more severe cases this can cause the top of the skull to be pointed or cone-shaped (oxycephaly or turricephaly). When a baby has craniosynostosis, the pressure inside the brain can be assessed to ensure that the unusual shape of the skull is not putting undue pressure on the developing brain. Treatment may involve wearing a 'moulding' helmet or, if necessary, surgery.

A few babies have plagiocephaly, where baby's head is flat on one side, in several cases due to "wry neck" (torticollis). Plagiocephaly is most often treated with non-surgical methods such as positioning baby to sleep or rest to help reduce pressure on that side of the head or using a corrective helmet (Fukushima 1990; Martin 1990; Shur 2003; Pramparo 2005; Lalani 2006; Hiraki 2008; Tempesta 2008; Abdelhedi 2012; Le Tanno 2014; Yamamoto 2014; DECIPHER; Unique).

"Large fontanelle at birth - it was across his head and long and skinny. Did talk about maybe having to reopen [the bony plates] if they closed too early but everything was fine. They talked about him wearing a helmet but it wasn't needed." - 15q15.1q21.1 deletion, 10 years

"Fontanelle closed as expected. She has macrocephaly and plagiocephaly. The plagiocephaly was caused by development delay - not being able to sit until much later and lying on her head a lot. Tried to correct as a baby by lying on her side when possible. Not visible now as has very thick hair." - 15q21.2q21.3 deletion, 11 years

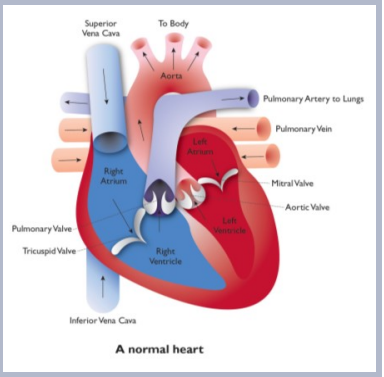
"Bones of skull fused as expected." - 15q21.3q22.2 deletion, 3 years

Skeletal anomalies/scoliosis

Concerns relating to the skeleton, including a sideways curvature of the spine (scoliosis), affect ~60% (six in 10) people with MFS, which is usually caused by mutations in the *FBN1* gene located in 15q21.1 (*see* Genes, page 35). Where scoliosis has been reported in association with 15q deletions, concerns appear to be more common in those with a deletion including the *FBN1* gene, although it is not a consistent feature. There are also several cases of scoliosis in those with a deletion that doesn't appear to include the gene, including two *Unique* members, one with a 15q21.2q21.3 deletion and the other with a 15q21.2q22.3 deletion.

Scoliosis can cause long-term backache and in more severe cases, where the curvature means the spine is pressing against the heart and lungs, it can make breathing difficult. Curvatures of the spine often develop or worsen with age and should be monitored carefully. If the scoliosis is mild, no

Heart conditions



A normal heart

Heart murmur: A heart murmur is an extra or unusual sound that is made by blood flowing through the heart and by the valves in your heart opening and closing. It may indicate an underlying heart problem, such as an ASD (see below), but often there is no cause at all. Often a heart murmur is "innocent", meaning there is no structural heart problem and no treatment is required.

Persistent ductus arteriosus (PDA): This is a channel between the aorta and the pulmonary artery that takes blood to the lungs, which usually closes shortly after birth. When it stays open, the lungs receive more blood than they should, and the heart has to work too hard. It can be closed, using minimally-invasive surgery, by inserting a coil via an artery in the thigh. Tissue grows around the coil, closing the gap.

Atrial septal defect (ASD): A hole in the muscular wall between the two filling parts of the heart (the atria). Some blood flows through from the left to the right side, increasing the amount of blood flowing to the lungs. Treatment depends on the type of defect, whether it closes spontaneously, and its size. Treatment can include medical management, taking medications to help the heart to work better, control of potential infection to the inner surfaces of the heart, and surgical repair with stitches or a special patch. Often ASDs will close spontaneously, without the need for surgery.

Ventricular septal defect (VSD): A hole in the wall between the two pumping chambers of the heart (ventricles) allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Specific treatment for VSD is determined individually. A baby with a VSD will be evaluated periodically. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from exposure to extra blood flow.

Mitral valve prolapse (MVP) and insufficiency: The mitral valve between the upper left heart chamber and the lower left chamber does not close well enough to prevent back flow of blood when the ventricle contracts. The flaps of the mitral valve allow blood from the left ventricle to flow back into the left atrium.

Persistent foramen ovale (PFO): An opening between the two upper chambers of the heart does not close in the first year of life, as would normally be expected. When it remains open, this allows extra blood to pass from the left to the right side of the heart.

Tetralogy of Fallot (ToF): A rare condition caused by a combination of four heart defects that are present at birth: VSD; pulmonary valve stenosis (narrowing of the pulmonary valve); right ventricular hypertrophy (thickening of the muscle of the right ventricle); and overriding aorta (the aorta isn't in its usual position coming out of the heart). This combination of defects means that the amount of oxygen in the blood is lower than normal.

Supraventricular tachycardia (SVT): A condition where the heart suddenly beats irregularly and faster than normal. It is not usually serious, but some people may require treatment.

Coarctation of the aorta (CoA): The main artery (the aorta) has a narrowing, which means that less blood can flow through it. Often requires surgical treatment shortly after birth.

treatment may be required but the curvature can be treated with physiotherapy and exercises, or a support brace may be needed. If the curve becomes marked it may be necessary to undergo spinal fusion surgery and straighten the spine using rods, as was the experience for one *Unique* member.

Rarely, a sunken chest (pectus excavatum) and a pigeon chest (pectus carinatum) have been observed. One *Unique* baby was born with a sacral dimple (a dimple or hole in the skin just above the crease between the buttocks). One boy with a 15q21.1 deletion including the *FBN1* gene had surgery at the age of 7 to correct his sunken chest and at the age of 12 to partially correct scoliosis (Faivre 2010; Hilhorst-Hofstee 2011; Colovati 2012; Dordoni 2017; DECIPHER; Unique).

"She has scoliosis. No treatment required but monitoring to make sure it doesn't worsen."- 15q21.2q21.3, 11 years

Heart conditions

A child with a chromosome disorder can expect to have a careful cardiac (heart) examination. This is particularly the case for babies with MFS because of the known link between this syndrome and weakening of the walls of certain blood vessels and valves within the heart.

While many babies and children we know about with a 15q deletion in this region had no heart condition, others, particularly those with 15q deletions that included the *FBN1* gene, had a heart condition(s) - often one characteristic of MFS. In these cases, the condition is often milder than when associated with classical MFS. Treatment may not be necessary but this will depend on the type and severity of any heart condition (*see* Heart Conditions, page 28).

Conditions characteristic of MFS usually affect the aorta (the main blood vessel that carries blood from the heart to the body) but may also affect the valves in the heart. Those reported in medical literature and among *Unique* members include incidences of a prolapsed (floppy) mitral valve (MVP) in the heart (one of the heart's valves which control the flow of blood through the heart doesn't close tightly enough) and aortic regurgitation (the aortic valve does not fully close meaning blood leaks back into the heart. This often happens when the aorta is enlarged). A few cases of other heart conditions have also been reported in association with 15q deletions in this region, including: holes between the upper or lower chambers of the heart (ventricular septal defects (VSD) or atrial septal defects (ASD)), which in many children heal (close) naturally without surgery; several cases of septal hypertrophy (the muscular wall (septum) between the ventricles is thicker than normal, which may block blood flow out of the heart); patent foramen ovale (PFO) (an opening between the two upper chambers of the heart does not close in the first year of life, as would normally be expected. When it

remains open, this allows extra blood to pass from the left to the right side of the heart); and a variant of a complex heart condition known as tetralogy of Fallot (TOF), in which the circulation to the lungs is reduced. TOF needs to be corrected surgically (Koivisto 1999; Shur 2003; Hutchinson 2003; Pramparo 2005; Ades 2006; Lalani 2006; Singh 2007; Faivre 2010; Colovati 2012; Dordoni 2017; DECIPHER; Unique).

“ No problems with the heart. Saw Cardiology but all was normal. ” - 15q21.2q21.3 deletion, 11 years

Brain anomalies & seizures

Magnetic resonance imaging (MRI) is a technique that can be used to visualise the brain. Interpreting findings from an MRI is the job of a paediatrician or paediatric neurologist. While many babies and children appear to be unaffected, in a few cases under MRI an anomaly of the brain has been observed in association with 15q deletion in this region.

In a few babies, the fluid-filled ventricles within the brain were somewhat larger than expected (ventriculomegaly). There were also several cases where the band of nerve fibres that links the right and left sides of the brain (the corpus callosum (CC)) were partially missing (agenesis (ACC)) or underdeveloped (hypoplastic (HCC). In most cases these are non-specific minor abnormalities that may be accidentally found in brain MRIs but do not have any consequence for the health of the child.

Seizures are caused by a change in electrical activity in the brain. It appears that there is a greater likelihood of experiencing seizures when a deletion includes the critical region in 15q22.2. Depending on the part(s) of the brain affected, symptoms vary but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Age of onset can vary considerably, and seizures may be isolated to a single incident or occur more regularly. Electroencephalograph (EEG) and video telemetry (video EEG) are medical tests that can be used to measure and record the electrical activity of the brain and are tools that, when used alongside other tests, can help diagnose the type of seizure experienced. Seizures can often be well-controlled with anti-epileptic drugs following diagnosis, including sodium valproate. Some children may have EEG abnormalities but no epileptic episodes; in such cases an anti-epileptic therapy is generally not required (Koivisto 1990; Shur 2003; Lalani 2006; Tempesta 2008; Papadopoulou 2010; Yamamoto 2014; DECIPHER; Unique).

“ There was a slight increase in the size of his brain ventricles at his 20 week scan. We had follow up scans at 26 and 32 weeks but they weren't overly concerned at the time. This has not been investigated since. He had myoclonic epilepsy in infancy from three months to ~16 months. We tried Clonazepam and Epilem which helped. He grew out of them around 16 months and has been medication free since. ” - 15q21.3q22.2 del, 9 years

“ Her MRI was read as normal by one doctor, but another saw something small related to the thickness or width of a connective tissue. Seizures began at 9 months. Her eyes would deviate up for less than a second. She was treated with Keppra, which stopped them very quickly and she was seizure-free for two years. She came off the medicine and after a while her seizures came back but Keppra wouldn't work. She now takes Epidilex and Clobazam, which work well. ” - 15q21.3q22.31 deletion, 8 years

“ No problems with kidneys, heart or brain. ” - 15q21.2q21.3 deletion, 11 years

“ No concerns. ” - 15q21.3q22.2 deletion, 3 years

Kidneys & urinary tract infections

The urinary tract is made up of the kidneys, bladder, ureters (the tubes that run from each kidney to the bladder) and the urethra (a single tube that carries urine out of the body).

Occasionally, anomalies of the urinary tract have been reported in medical literature and by *Unique* families, including several cases of hydronephrosis. Hydronephrosis is a condition where one or both kidneys become stretched and swollen as the result of a build-up of urine inside them. This can lead to an increased chance of a child developing urinary tract infections (UTIs). In more severe cases that remain untreated it can result in damage to the kidney(s). One cause of hydronephrosis is megaureter, where one or both of the ureters is larger than normal, and this was the case for a few children with a 15q deletion in this region. Boys are more likely than girls to have a megaureter.

One boy had urinary reflux, where one or both of the valves at the meeting point between each ureter and the bladder doesn't work properly, causing urine to back up (reflux) from the bladder to the kidney.

The need for treatment will depend on the nature of the condition. UTIs may require treatment with antibiotics, which is usually very effective. Very occasionally, a catheter may need to be inserted to remove the build-up of urine and prevent damage to the kidney(s) (Shur 2003; Lalani 2006; Abdelhedi 2012; DECIPHER; Unique).

“ No kidney concerns so far but we have to have this checked every few years. ” - 15q21.3q22.31 deletion, 8 years

Eyes & Vision

Many babies and children with a deletion involving this region of chromosome 15 were found to have an eye or vision anomaly(ies).

Most common was a squint (strabismus), which occurs when one or both eyes turn inward, outward, up or down, and appears to occur more frequently when a deletion includes 15q22.2. A squint may be constant or it

can occur intermittently, especially when tired. Interventions like patching, exercises or glasses generally work well to correct a squint, but for some it may only be corrected following a surgical operation. Several children developed a "lazy eye" (amblyopia), which can be a consequence of a constant squint in one eye.

Some children had a degree of short-sightedness (myopia) or long-sightedness (hyperopia) and a few had astigmatism, leading to blurred vision. Where necessary, individuals may benefit from wearing glasses.

There have been at least two cases of blepharophimosis, where the eyelids are underdeveloped leading to a narrowing of the eye opening, and several cases of nystagmus (uncontrolled eye movements) (Martin 1990; Pramparo 2005; Lalani 2006; Hiraki 2008; Tempesta 2008; Colovati 2012; Yamamoto 2014; Velázquez-Wong 2015; DECIPHER; Unique).

"He is long-sighted and has a squint and a lazy eye. Saw an ophthalmologist yearly and had patching and wears glasses." - 15q21.1q22.2 deletion, 9 years

"She is long-sighted and has strabismus and nystagmus." - 15q21.3q22.3 deletion, 8 years

Hearing

Hearing appears to be generally unaffected, but a few children have experienced some degree of hearing loss. Temporary fluctuating hearing loss caused by glue ear (a build-up of sticky fluid within the ear) can often be relieved by the insertion of tubes (grommets) to reduce pressure in the middle ear. Some children are particularly prone to ear infections, which can be very painful and debilitating. Treatment of ear infections with antibiotics and/or grommets may be necessary (Unique).

"Hearing screen: passed right ear but failed left ear. Had a follow up test which he passed. He has had occasional ear infections." - 15q21.3q22.2 deletion, 9 years

"No concerns about hearing." - del 15q25.2q25.3, 8 years

Hands & feet

Anomalies of the hands and feet are widely reported in those with a deletion involving 15q15 to 15q22, regardless of deletion size. Most common among these are a single crease across the palm; "puffy" hands and feet; small hands and feet; fingers (clinodactyly) or toes that curve inward; broad toes or thumbs; and flat (pes planus) or rocker bottom (congenital vertical talus) feet. Those with deletions including the *FBN1* gene may also have unusually long, tapering fingers (arachnodactyly). Many of these features are minor, non-functional anomalies and treatment for these conditions is generally not needed or they can be corrected passively. For others, treatments such as

insoles to help create an arch, physiotherapy or surgery may be employed, depending on the severity. Hypermobile joints may also make walking more difficult (Martin 1990; Fukushima 1990; Koivisto 1999; Shur 2003; Hutchinson 2003; Liehr 2003; Hiraki 2008; Pramparo 2005; Lalani 2006; Tempesta 2008; Faivre 2012; Abdelhedi 2012; Colovati 2012; Dordoni 2017; DECIPHER, Unique).

“ Puffy hands and feet. Short fingers. ” - 15q15.1q21.1 deletion, 10 years

“ Overlapping 4th and 5th toes, curved toes and flat feet. He saw a podiatrist when he was around two years old. They made orthotics which helped him to start walking and he continues to wear orthotics in his shoes. ” - 15q21.2q21.3 deletion, 11 years

“ Some toes not straight and very flat footed. Also has a bone fusion in the ankles so not much flexibity and walks with turned out feet. Unable to correct with othodics. ” - 15q21.2q21.3 deletion, 11 years

“ No unusual features. ” - 15q21.3q22.2 deletion, 3 years

Anomalies of the genitals

Fairly minor genital anomalies are quite common in children with a chromosome disorder, including those with a deletion involving the 15q15 to 15q22 region. The most common condition reported is undescended testicles at birth (cryptorchidism); however, the teste(s) may move to the correct position in the scrotum within the next few months. Treatment for this condition is therefore usually a combination of watchful waiting, with surgery to bring the testicles down if necessary (orchidopexy). The genitals of boys and girls may be very small. Occasionally the hole usually at the end of the penis is found on the underside instead (hypospadias); this is usually corrected surgically (Fryns 1982; Yip 1986; Fukushima 1990; Koivisto 1999; Papadopoulou 2010; DECIPHER; Unique).

Two men in their thirties with a very short 15q15.3 deletion were found to have reduced fertility, probably due to the deletion of the *CATSPER2* gene which is located in this band. The *CATSPER2* gene provides instructions for producing a protein that is found in the tail (flagellum) of sperm cells. When one copy of this gene is deleted, as in these cases, the affect is less than if both copies are deleted (*see* Genes, page 35) (Jaiswal 2014).

Hernias

Two *Unique* babies were born with a hernia, where an organ or fatty tissue pushes through a weak spot in a surrounding muscle or tissue. Hernias may heal naturally without the need for treatment, but in the majority of cases surgical repair is usually required. In one case the hernia was at or near the belly button (an umbilical hernia) and closed naturally around six to seven months after birth. The other case affected the inner groin (an inguinal hernia) and required surgery (Unique).

Hypersalivation & drooling

Several *Unique* parents mentioned that their child experienced excessive saliva production (hypersalivation) and/or drooling (sialorrhea), which tended to improve with age. Drooling can happen without excessive saliva production if there is difficultly keeping the mouth closed or there is an inadequate mechanism or rate of swallowing, as is sometimes the case with neurological conditions such as cerebral palsy and intellectual disability. Various treatment options are available and medication may be prescribed if necessary (Unique).

“ As a baby she hyper-salivated. It would cause skin irritation on her chin and she would often wear a bib. She can drool at times now but not often. ” - 15q21.2q21.3 deletion, 11 years

“ Excessive drooling - has become slightly better with age but it is still an issue. ” - 15q21.3q22.2 deletion, 9 years

Skin

Children with 15q deletions including the *FBN1* gene may have minor skin conditions typical of classical MFS. These may include skin that is more stretchy than normal, or a build-up in the levels of keratin in hair follicles resulting in small, white skin lesions. A few *Unique* babies and children had eczema. Your doctor should be able to recommend self-care techniques, emollients and other treatments that may help to relieve symptoms (Hilhorst-Hofstee 2011; Dordoni 2017; Unique).

Teeth & palate

In *Unique's* experience, dental concerns are common in children with a chromosome disorder and may be exacerbated by anomalies of the palate. Information is limited, but concerns have been reported among children with a deletion involving 15q15 to 15q22. *Unique* parents mentioned delayed tooth eruption, unusually broad teeth and gaps between the teeth. One 10-year-old had missing teeth, including the canines. Crowded teeth (dental crowding) is a feature of MFS and was reported for several children with deletions including the *FBN1* gene in medical literature. Children may have a high-arched palate (domed roof of the mouth) and/or an undersized jaw (micrognathia) - both features of MFS. A few children have a receding jaw (retrognathia). These features can have an impact on feeding, hearing, tooth alignment and speech.

A high standard of dental care is important to minimise damage by decay and erosion and children may require orthodontic treatment (Faivre 2010; Abdelhedi 2012; Colcovati 2012; Dordoni 2017; DECIPHER; Unique).

Genes

An individual deletion involving 15q15 to 15q22 will include a particular set of genes and other important regulatory sequences that control the process by which specific genes are "switched on" (gene expression). The function of a gene and its relevance to the outcome for the person with the deletion is not always known. New information is constantly emerging and will help with further understanding of these deletions.

The possible role of a few genes that are included in known deletions include:

FBN1 (Fibrillin 1)

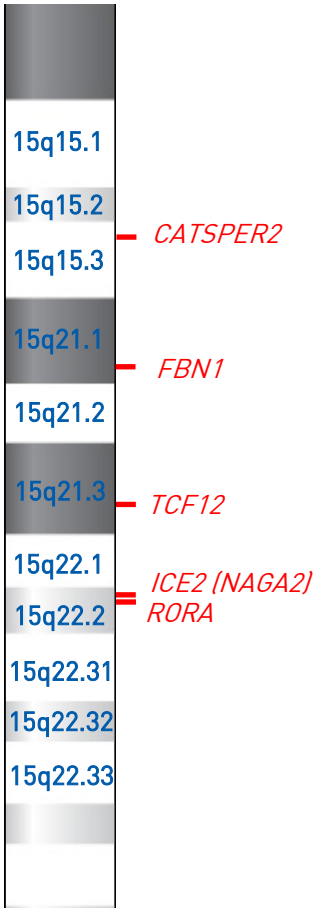
also known as: FBN; FBN1_HUMAN; MFS1; SGS

Location: 15q21.1

[48,408,313 - 48,645,709 (GRCh38/hg38) (from NCBI - Feb 2022)]

[48,700,510 - 48,937,906 (GRCh37/hg19) (from NCBI - Feb 2022)]

The *FBN1* gene is located near the distal end of band 15q21.1 and provides the instructions for making a large protein called fibrillin-1. Fibrillin-1 is involved in the formation of structures called microfibrils, which play a role in the formation of connective tissues. These tissues are found throughout the body and help hold together cells, tissues and organs, ensuring the body grows and develops properly.



Based on GrCh38/Hg38. Locations of genes will be different on older genome assemblies. Not to scale.

Micofibrils form elastic fibres in the skin, blood vessels and ligaments allowing them to stretch. They are also essential for providing support for bones, nerves, muscles and the lenses of the eye, which need to remain rigid.

Changes in the *FBN1* gene (variants) are responsible for most cases of Marfan syndrome (MFS). When a 15q deletion includes the *FBN1* gene additional features associated with MFS may also be observed, over and above those classically associated with these deletions (Hilhorst-Hofstee 2011; Dordoni 2017).

TCF12

also known as: bHLHb20; CRS3; HEB: HsT17266; HTF4; TCF-12

Location: 15q21.3

[56,918,090 - 57,292,595 (GRCh38/hg38) (from NCBI - Feb 2022)]

[57,210,288 - 57,583,508 (GRCh37/hg19) (from NCBI - Feb 2022)]

TCF12 is a gene that encodes a transcription factor - a type of molecule that controls the expression of other genes. TCF12 interacts with another protein called TWIST1. Together they play a role in ensuring the bones that make up the skull fuse together correctly during development of the embryo. A condition called craniosynostosis (*see* Head shape, page 26) occurs when this process goes wrong and the skull is not able to grow at the same rate as the developing brain. This can lead to a build-up of pressure which needs to be treated urgently in order to prevent damage to the brain that may result in conditions such as developmental delay, seizures and cognitive impairment.

Some cases of craniosynostosis are the result of variants and deletions involving *TCF12* but because there is so-called "incomplete penetrance" many babies with a mutation or deletion involving *TCF12* do not develop craniosynostosis. There is also variation in the severity of cases where craniosynostosis does occur (Hiraki 2008; Le Tanno 2014; Sharma 2013; Yamamoto 2014; Piard 2015).

CATSPER2

also known as: cation channel sperm-associated protein 2; cation channel, sperm associated 2; CTSR2_HUMAN; sperm ion channel

Location: 15q15.3

[43,628,503 - 43,684,884 (GRCh38/hg38) (from NCBI - Feb 2022)]

[43,920,701 - 43,941,082 (GRCh37/hg19) (from NCBI - Feb 2022)]

The *CATSPER2* gene produces a protein that is found in the tail of sperm cells. This protein plays a role in sperm cell movement and allowing the sperm cell to enter and fertilize an egg cell during conception.

When the 15q15.3 region of chromosome 15 is deleted on ***both*** chromosomes, meaning both copies of a number of genes in this region are deleted, including *CATSPER2*, this causes a very rare syndrome called deafness–infertility syndrome (DIS). In these cases, where both copies of the *CATSPER2* gene are deleted, no CATSPER2 protein is produced. This means that sperm will have a decreased motility and are unable to push through the membrane of the egg cell, which is necessary to achieve fertilisation, leading to infertility. In addition, the absence of proteins produced by other genes in the region results in hearing loss and a type of anaemia.

The deletions described in this guide involve the deletion of only ***one*** copy of 15q15.3. This means that in addition to other concerns, boys with a deletion including *CATSPER2* may have a less severe condition characterised by infertility but not deafness or anaemia (Knijnenburg 2009; Jaiswal 2014).

RORA (RAR-related orphan receptor A gene)

also known as: bHLHb20; CRS3; HEB: HsT17266; HTF4; TCF-12

Location: 15q22.2

[60,488,284 - 61,229,302 (GRCh38/hg38) (from NCBI - Feb 2022)]

[60,780,483 - 61,521,501 (GRCh37/hg19) (from NCBI - Feb 2022)]

Variants (changes) in the *RORA* gene cause a syndrome called Intellectual Developmental Disorder with or without Epilepsy or Cerebellar Ataxia (IDDECA). It has been proposed that deletion of this gene plays a role in the intellectual disability, seizures and ASD associated with deletions involving 15q22.2 (Yamamoto 2014; Guissart 2018).

ICE2

Formerly known as: **NARG2**

also known as: BRCC1, FLJ11896, ENSG00000128915

Location: 15q22.2

[60,419,609 - 60,479,142 (GRCh38/hg38) (from NCBI - Feb 2022)]

[60,711,808 - 60,771,341 (GRCh37/hg19) (from NCBI - Feb 2022)]

The *NARG2* gene is expressed at high levels in the brain in the early stages of development. It has been suggested that deletion of this gene could be linked to intellectual disability associated with deletions involving 15q22.2 (Yamamoto 2014).

Websites

www.patient.info - information on medical conditions and terms

www.nhs.uk/conditions/ - easy to understand explanations of medical conditions and procedures

www.marfantrust.org - Marfan Trust - a UK-based charity that provides support and information for those with Marfan syndrome

www.marfan.org - The Marfan Foundation –a US-based non-profit organisation that provides information and support for individuals with genetic aortic and vascular conditions, including Marfan, Loeys-Dietz, and Vascular Ehlers-Danlos syndromes

DECIPHER

This guide makes use of data generated by the DECIPHER community. A full list of centres who contributed to the generation of the data is available from http://decipher.sanger.ac.uk and via email from decipher@sanger.ac.uk. Funding for the project was provided by the Wellcome Trust.

The DECIPHER database is used by clinicians and researchers to report and share anonymised patient records containing the details of key genetic changes and their associated clinical features. This sharing of information helps to increase the knowledge and understanding of each genetic change and whether it is causal for the clinical features; this improves the quality of advice that can be given to those with the same or similar genetic changes. Patients give their consent to allow their linked-anonymised data to be openly shared. Sharing records openly in a database such as DECIPHER may increase the opportunity for patients with very rare conditions to participate in research or trials of new therapies.

DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources. Firth, H.V. et al (2009). Am.J.Hum.Genet 84, 524-533 (DOI: dx.doi.org/10/1016/j.ajhg.2009.03.010)

Notes

Inform Network Support

Rare Chromosome Disorder Support Group

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info@rarechromo.org | www.rarechromo.org

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