Understanding Chromosome & Gene Disorders

15q25 deletions

(15q25.2 microdeletion syndrome)

rarechromo.org

15q25 deletions

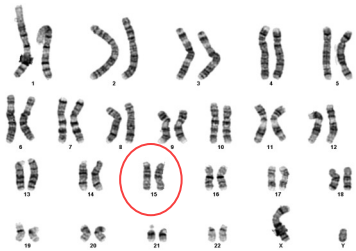
A chromosome 15q25 deletion is a rare genetic condition in which there is a missing (deleted) copy of part of the genetic material that makes up one of the body's chromosomes - chromosome 15. As with other chromosome disorders, having a missing piece of genetic material may increase the risk of congenital disorders (birth defects), affect the development and intellectual abilities of a child and be associated with a range of other individual features, to a varying degree. It is important to remember that the outcome of having a 15q25 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.

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.

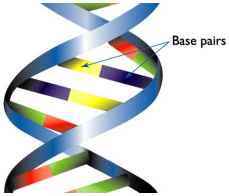
Apart from the sex chromosomes (usually two Xs for a girl and an X and a Y for a boy), chromosomes are numbered 1 to 22, approximately from largest to smallest.



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

Looking at chromosome 15

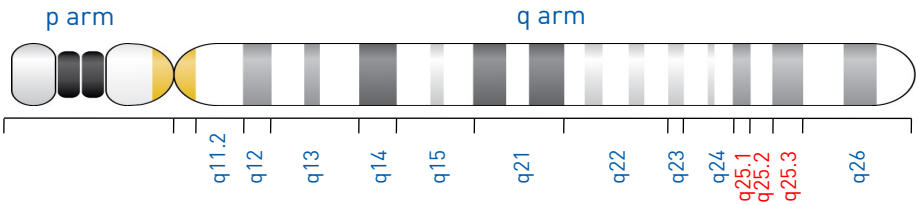
Each chromosome contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. There are millions of base pairs in every chromosome, and they are often counted in millions, where 1 Mb equals one million base pairs. The whole 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

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



Each chromosome has a short (p) arm and a long (q) arm. The bands are numbered outwards starting from the point where the short and long arms meet (the centromere) (marked in yellow). A low 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. 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.

People with a 15q25 deletion have one unaffected chromosome 15, but the other chromosome 15 has chromosomal material missing from part of band 15q25 on the long arm, which is divided into three sub-bands: 15q25.1, 15q25.2 and 15q25.3 (marked in red). Some people also have larger deletions that extend into other bands e.g. 15q23,15q24,15q26.

The majority of individuals with a 15q25 deletion have a deletion involving 15q25.2. Although cases are still rare and data is limited, the main focus of this guide will therefore be on a novel 15q25.2 microdeletion syndrome that has been described the in medical literature (OMIM #614294) (Mefford 2007; Wagenstaller 2007; Itsara 2009; Wat 2010; Cooper 2011; Palumbo 2012; Doelken 2013; Burgess & Brown 2014; Chen 2020; DECIPHER database).

Sources

The information in this booklet is drawn from published medical literature and information from *Unique* members. The first-named author and publication date from 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. Seven *Unique* members completed a detailed survey in 2020. 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) in order to produce the billions of cells that are necessary for human growth and development. Changes to the structure of chromosomes often occur during the cell divisions that lead to the creation of egg or sperm cells.

During this complicated process, chromosomes arrange themselves in their 23 pairs, with pairs lying alongside each other, apart from the sex chromosomes X and Y which attach to each other at both ends. The chromosomes in a pair 'recognise' each other because they are similar. Segments of DNA are then exchanged in a process known as crossing-over (recombination) and the chromosomes are held together at the crossing points (known as chiasmata). Where the DNA in a chromosome is repeated at close intervals (called low copy repeats (LCR)), "mistakes" may occur during this process, leading to parts of a chromosome(s) being lost, duplicated and/or becoming rearranged.

Most of the DNA that makes up chromosome 15q is present as a unique sequence, but many of the chromosomal rearrangements involving chromosome 15q25.2 are thought to be due to the presence of at least four such LCR in this region, where the DNA sequence is repeated at close intervals, which make it a "hotspot" for errors during the formation of sperm and egg cells. These repeated sections are in band 15q25.2 (LCR-**A**, LCR-**B** and LCR-**C**) and in band 15q25.3 (LCR-**D**) (*see* diagram on pg 31).

The presence of these LCR can mediate a process called non-allelic homologous recombination (NAHR) leading to the deletion of the segment of chromosome that lies between the LCRs involved. So, depending on the LCRs involved, a 15q25.2 deletion may involve:

- the more proximal region of 15q25.2, when there is a deletion between LCR-A or B and LCR-C
- the more distal region of 15q25.2 and the proximal part of 15q25.3, when there is a deletion between LCR-C and LCR-D
- both the proximal and distal regions of 15q25.2 and the proximal part of 15q25.3 when there is a deletion between LCR-A or B and LCR-D.

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. While both proximal and distal deletions are associated with some degree of intellectual disability and developmental delay, more recently additional features associated specifically with either proximal or distal deletions have been assigned (*see* Common Features, pg 11). Of note, when researchers compared the features most common to

patients with deletions involving only the proximal region of 15q25.2 with those who have deletions involving both the proximal and distal regions there didn't appear to be many additional features. This suggests that the loss of genes within the more proximal region of 15q25.2 is responsible for the majority of the features associated with 15q25.2 deletions (Mefford & Eichler 2009; Wat 2010; Palumbo 2012; Doelken 2013; Burgess & Brown 2014).

Genetic tests

With any deletion the amount of deleted DNA can vary. Deletions that are so small that they are not visible under the microscope using standard techniques, as is the case for many deletions involving 15q25, 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 deletions 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 (and microduplications) 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 after fertilisation. Usually, this means that one "population" of cells containing a 15q25 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 symptoms.

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 but where it has been reported in medical literature for other rare chromosome disorders, the outcome of the condition was in some cases milder.

In 2020, *Unique* had one member with a rare type of mosaicism. Unusually, while one chromosome 15 in all the cells tested had a deletion involving 15q25.2 extending into 15q25.3, in this case mosaicism arose not because some cells had a "normal" chromosome number and arrangement but because some cells also had an additional deletion involving another region of 15q25.2.

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 including 15q25 might have results that look like one of these examples:

46,XY,del 15q25.2 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 means there is missing material (a deletion). 15q25.2 shows the part of the chromosome that is deleted; in this case, the missing material comes from the long (q) arm of chromosome 15 in band q25.2.

arr[hg19] 15q25.2q25.3(83214257_85794656)x1 dn This result shows that the analysis used microarray technology (arr). The analysis revealed a DNA anomaly involving 15q25.2q25.3. 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 83214257 and 85794656 (by taking the first number from the second, you can work out that this is 2,580,399 base pairs, or 2.58 Mb). There is a missing copy (x1; the normal copy number is two) so it is a deletion. hg19 tells you which version of the human genome was used for comparison (*see* Genome Assemblies (blue box)). 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.

mos 46,XX,del 15q25.2,[19]/46,XX,[11] This would be an example of mosaicism (mos), meaning that different cells in this individual have different numbers or arrangements of chromosomes. This is a girl or woman (XX). Thirty cells have been tested. Nineteen ([19]) cells had a deletion of chromosome 15 (del 15). q25.2 shows the part of the chromosome that is

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 duplications 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 starting to use 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.

deleted; in this case, there is a loss of a chromosome segment in q25.2. Eleven [11] cells showed a normal karyotype for a girl or woman (46,XX) and didn't have the deletion.

You may wish to compare your child's 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 15q25 deletions?

It is difficult to estimate the prevalence of 15q25 deletions since many people will not have been diagnosed, and many of those who are diagnosed are not reported. We do know that at the time of writing, more than 20 individuals with a 15q25 deletion involving 15q25.2 had been reported in medical research articles, and there were a similar number of cases listed in the DECIPHER database. *Unique* had eight members with a deletion affecting

15q25.2 alone; seven with a deletion involving 15q25.2 and 15q25.3; and two with a 15q25 deletion for which the precise bands involved were not detailed. *Unique* also had members with deletions extending into 15q26 (three with a 15q25.3q26.1 deletion; one with a 15q25.3q26.2 deletion; one with a 15q25.1q26.2 deletion; and one with a 15q25.3q26.3 deletion) (Mefford 2007; Wagenstaller 2007; Itsara 2009; Wat 2010; Cooper 2011; Palumbo 2012; Doelken 2013; Burgess & Brown 2014; Chen 2020; DECIPHER database; Unique).

Note: All these numbers include only those individuals with no other known genetic anomaly(ies). *Unique* also has further guides to 15q deletions that may be useful to members with larger 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.

15q25 deletions are known to be either inherited from a parent or to occur *de novo* (dn), which means the deletion has occurred as a new event in the child. While for many the origin of the deletion was unknown, the vast majority of deletions where the origin is known appear to have arisen *de novo*, with just a few cases of deletions inherited from a parent.

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 15q25 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 15q25 deletion or any other chromosome disorder. Very rarely (less than 1%), both parents have unaffected chromosomes by a blood test, but a few of their egg or sperm cells carry a chromosomal change. 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 15q25 deletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 15q25 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. Your genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a 15q25 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.

Are there people with a 15q25 deletion who are healthy, have no major medical problems or birth defects and have developed normally?

Yes. The DECIPHER database lists several cases of tiny microdeletions inherited from a seemingly unaffected parent, including two girls, one with a 467.37 kb 15q25.1 microdeletion and one with a 171.76 kb 15q25.2 microdeletion. For many of the entries in DECIPHER where a deletion of 15q25 is reported, the significance and/or contribution of the 15q25 deletion to any observed feature is also listed as unknown or uncertain.

Since several people with a 15q25.2 deletion involving the distal region didn't exhibit the features commonly associated with these deletions, including a boy with a 604 kb 15q25.2q25.3 microdeletion whose father with the same deletion was unaffected, it has also been suggested that distal deletions of 15q25.2 can show "reduced penetrance" (*see* blue box). One *Unique* member, who requested that her 14-year-old daughter was tested only because she was smaller than all her peers and experienced delayed puberty, was subsequently found to have the same deletion as her daughter. Another family requested that their 9-year-old son was tested due to autistic features and a tendency to over-eating. Further investigation revealed that the

Variable expressivity refers to the range and severity of features that occur in different people with the same genetic change (e.g. a duplication, deletion or gene mutation). For each feature, some people may not be affected or may be only very mildly affected; others may be more severely affected.

Penetrance refers to the proportion of people with a particular genetic change who exhibit any sign or symptom of that genetic disorder. If everybody with a particular genetic change is affected in some way, the condition is said to have **complete penetrance.** If some people don't develop any of the features associated with the disorder, the condition is said to have **reduced (incomplete) penetrance**.

Both these phenomena can make it extremely challenging to provide accurate genetic counselling, since it's not possible to accurately predict how future generations in a family with a particular genetic change might be affected. *See Unique*'s guide to "Variable Expressivity & Reduced Penetrance" for more details.

deletion had been inherited and led to testing of those of their children who also displayed autistic traits, who were subsequently found to have also inherited the deletion and were affected to a lesser but variable degree.

Reduced penetrance has not been suggested for proximal 15q25.2 deletions (Cooper 2011; Doelken 2013; Hyon 2016; DECIPHER, Unique).

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 14 years - usually as the result of delayed growth, a delay in reaching developmental milestones or health concerns. One *Unique* baby was diagnosed prenatally with a congenital diaphragmatic hernia (CDH) (*see* Anomalies of the chest & abdomen).

“ He was diagnosed at six years; he had several phenotypic indicators of genetic anomalies, developmental delay, and a heart condition (ventricular septal defect (VSD)). The diagnosis was helpful because it was easier to get an autism diagnosis and be found eligible for special services. ” - del 15q25.2q25.3, 19 years

“ He was tested and diagnosed at eight years due to speech and cognitive development delay, a high-arched palate and hammer toes. ” - del 15q25.2q25.3, 13 years

Common Features

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.

The main features of 15q25 deletion syndrome, involving a 660 kb deletion within a hotspot in chromosome 15q25.2 to 15q25.3, often occur in this way. These features are thought to result from the deletion or disruption of a number of genes within 15q25. In recent years our understanding of the genes that may be involved has increased (*see* pg 31) but there is still a lot that we don't know.

It is important to remember that just as “typically”-developing children can experience a number of unforeseen physical and behavioural difficulties, each person with a 15q25 deletion is unique and the developmental and medical concerns they experience vary from person to person. However, the most common features associated with 15q25 deletions, 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 on the next page.

Common features of 15q25 deletions:

- Some degree of developmental delay (often mild to moderate)
- Some degree of intellectual disability/learning difficulty
- Short stature after birth
- Hypotonia (low muscle tone)
- Anomalies affecting the chest and abdomen, including congenital diaphragmatic hernia (CDH), inguinal (groin) hernia and pectus excavatum (funnel chest)
- Anaemia
- Thrombosis
- Heart conditions
- Cryptorchidism (undescended testes)
- Primary ovarian insufficiency (POI)
- Mild but variable (unusual) facial features
- Neuropsychiatric disorders (likely to be more common in individuals with deletions including the distal region)
- Seizures (likely to be more common in individuals with deletions including the distal region)
- Strabismus (a squint) (likely to be more common in individuals with deletions including the distal region)

(Mefford 2007; Wagenstaller 2007; Itsara 2009; Wat 2010; Cooper 2011; Palumbo 2012; Doelken 2013; Burgess & Brown 2014; Chen 2020; DECIPHER; Unique)

Pregnancy & Birth

The information we have is limited, but suggests that pregnancy and birth were often routine. In some cases, parents told us about complications that were picked up during routine pre– or post-natal screening. These included reduced growth, reduced foetal movements, a heart condition or a hernia. A few babies were delivered early by caesarean section.

Where we have information, in almost all cases birth weight, length and head circumference measurements were within the normal range, although a few babies grew slowly in the womb and were small at birth.

“ Born full term after healthy pregnancy. ” - del 15q25.2q25.3

“ Diagnosed prenatally at 16 weeks with a congenital diaphragmatic hernia and had scans every three weeks throughout pregnancy. Operated on at birth and spent 2.5 months in hospital. ” - del 15q25.2

New-born babies

While a significant number of babies experienced some degree of difficulty in the new-born period, others had a more routine delivery and post-natal period. Some babies had feeding difficulties and several were diagnosed with congenital anomalies. A baby girl was intubated and ventilated for four days immediately after delivery before being treated for a week by continuous positive airway pressure (CPAP) to keep her airways open. She was also successfully treated with iron supplements for iron deficiency anaemia and phototherapy for jaundice. A baby boy was brought to hospital at three weeks of age with failure to thrive and was diagnosed with an atrial septal defect (ASD) and a large ventricular septal defect (VSD), which were surgically repaired successfully (*see* Heart Conditions, pg 26) (Palumbo 2012; Doelken 2013; Burgess & Brown 2014; Unique, DECIPHER).

“ After an uneventful pregnancy with normal scans, he was born at 37 weeks with a normal delivery and no breathing or feeding problems. ” - del 15q25.2

“ She was small and pale at birth. She did not keep down her milk and had a lot of diarrhoea. At three months it was discovered that her haemoglobin was low and she had blood transfusions because she did not have enough red blood cells. She had a lot of childhood infections, including chest infections and pneumonias. After the first blood transfusion she improved and she began to feed herself but still had diarrhoea, so we tried milk without lactose. The diarrhoea was still there but no more vomiting. The infections continued and eventually a different doctor saw her and put her on antibiotics, after which she improved a lot. Her haemoglobin levels were checked frequently and she took daily corticosteroids and was seen by a haematologist, endocrinologist and neurologist. There are still concerns but she is ill less often and now has fewer problems. ” - del 15q25.2, 3 years 10 months

Growth & Feeding

A few babies were born small for gestation and remained small, but many babies were born within the normal range for growth parameters at birth. While some babies and children continued to maintain a healthy growth rate within normal limits for the child population, for others growth rates subsequently slowed and in some cases became extremely pronounced so children were very short.

In medical literature, a boy with a birth weight on the 90th centile (the top 10% of the population) experienced a severe slowdown in growth, and when measured at 11 months had weight, height and head circumference measurements well below the 3rd centile (the lowest 3% of the population). A similar but less severe postnatal growth restriction was observed in a boy of nearly three years. A boy with a birth length on the 25th centile who was

assessed at 17 years of age had average weight and head circumference measurements but was only just over 5ft tall. His lack of height was not the result of a deficiency in growth hormone. A 14-year-old girl was small for her age and had the bone age of a 12-year-old. Among *Unique* families, a similar picture was observed. Survey data suggests that most children were of average or below average height and average or sometimes above average weight. One *Unique* child was receiving growth hormone treatment.

"Growth delay but in proportion. At two-and-a-half years she looked more like a 10-month-old and was the same shoe size for a year. At three years, she is still small for her age (more like a two-year-old), but her feet are now growing as expected." - del 15q25.2

"A well-thriving child. At four years his height is 99.75cm (25th centile) and his head circumference is 50.5cm (25th)." - del 15q25.2

Feeding difficulties, especially in the new-born period, are common among babies with a rare chromosome disorder. Although some parents told us that their baby had no early feeding difficulties, for others feeding was more challenging. Problems were often temporary, but in a few cases difficulties led to poor weight gain and, very rarely, failure to thrive.

A few babies suffered from 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, occasionally for an extended period.

Longer term, a few *Unique* children had a very limited diet and some may have had sensory issues around food. A 12-year-old boy had swallowing syncope, where immediately after a person swallows food they faint or pass out, and required monitoring. For babies with early feeding difficulties, it 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.

In medical literature there is limited data, but a 9-year-old girl with a 1.65Mb 15q25.2 deletion had difficulties feeding as a baby as a result of generalised low muscle tone (hypotonia) which made sucking difficult. Subsequently, these problems resolved and she had an average weight between the 25th and 50th centiles by the age of seven years. A baby girl with a 2.5Mb deletion experienced GERD with aspiration, where the stomach contents return up

the food passage and some of the refluxed liquids enters the lungs, and continued to require nasogastric tube feeds at five months, when she was last assessed (Wagenstaller 2007; Palumbo 2012; Doelken 2013; Burgess & Brown 2014; Chen 2020; Unique; DECIPHER).

“ Poor appetite. At seven years he was recently diagnosed with a rare stomach condition which may require him to have a stomach PEG. Awaiting endoscopy and colonoscopy. ” - del 15q25.2

“ She had difficulties with adjusting to using a sippy cup or liquids other than milk, so used a bottle for longer. She is now able to use a sippy cup and has no problems with eating, although she eats relatively small portions. ” - del 15q25.2, 3 years

“ VERY picky eater. Eats from a very limited menu and is very particular about the texture of food. ” - del 15q25.2q25.3, 19 years

Appearance

There may be little sign in the appearance of babies and children with a 15q25 deletion of the underlying disorder. Doctors may notice what are known as dysmorphic (unusual) features and you may notice similarities with other children with a comparable deletion.

Among children with a 15q25.2 deletion, low-set ears or unusually-shaped ears were the most commonly noted feature and at least five children had a webbed neck (pterygium coli). Other unusual features have been described, including a bulge down the middle of the forehead or prominent forehead; narrow or almond-shaped, up-slanting eyes; a small nose with thick nostrils; a broad nose with prominent nasal ridge; a triangular-shaped face; a thin upper lip or exaggerated triangular-shaped upper lip; and a small or receding jaw (Palumbo 2012; Doelken 2013; Burgess & Brown 2014; Unique; DECIPHER).

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

There appears to be considerable variability in the extent to which gross motor skills are affected in babies and children with a 15q25 deletion. Some developed motor skills such as rolling, sitting and walking around the same age as “typical” children; others experienced some degree of delay, usually mild to moderate, which sometimes showed a marked improvement with time. Some babies and children had reduced muscle tone (hypotonia), which can make a baby or child feel floppy to handle and make achieving mobility milestones more difficult, although muscle tone often improves with age. Even where gross motor skills were unaffected, some experienced problems with hand use and co-ordination (fine motor skills - *see* pg 15) and/or some degree of intellectual disability or learning difficulty (*see* pg 16). A similar

Completing the balance parts of an obstacle course for the first time!

picture was seen among *Unique* members and in medical literature.

In medical literature, cases ranged from a girl who learned to walk at almost four years, to a five-year-old boy who sat independently at six months and walked independently at two years with an unsteady and wide gait, and a boy who sat independently at six months, crawled at nine months and walked independently at 15 months (Wagenstaller 2007; Wat 2010; Palumbo 2012; Doelken 2013; Burgess & Brown 2014; Chen 2020; DECIPHER; Unique).

Regular physiotherapy (PT) often proves 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 help increase mobility.

“ Developmental delay: behind average with all milestones. ” - del 15q25.2q25.3

“ Has not affected his physical development. Developmental milestones were reached within the normal timeline: sitting at 6/7 months, crawling at 10/11 months and walking at 14 months. Reading and writing are delayed. ” - del 15q25.2q25.3, 13 years

“ No developmental delay or intellectual disability. Attends a mainstream school. ” - del 15q25.2q25.3 mat, 16 years

“ Has developmental delay. Low muscle tone, hypermobile joints and scoliosis make movement difficult. Started bottom shuffling at about two years and is making progress. She can stand up with special shoes and support and has physiotherapy. ” - del 15q25.2, 3 years

“ Delayed in all motor skills but good catch up. ” - del 15q25.2q25.3 mat

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

Information relating specifically to fine motor skills is scant, but some degree of difficulty with hand use and hand-eye coordination appears to be common among *Unique* children, and these skills don't necessarily develop in line with gross motor skills. Fine motor skills are essential for tasks involving holding and handling objects such as holding a bottle, using cutlery, playing with toys, holding a pencil and fastening clothes. Early intervention with occupational therapy to stimulate hand use can prove extremely

beneficial. Jigsaws, Lego, dot-to-dot pictures, peg boards and shape-sorters can all be helpful (Unique).

“ Has good handwriting, but has a hard time using utensils, like a knife, to cut up food. ” - del 15q25.2q25.3, 19 years

“ He struggles mainly with writing, laces, and using cutlery. ” - del 15q25.2q25.3 mat, 12 years

Ability to learn

There is considerable variability in learning ability. For some, learning appears to be unaffected while for others some degree of learning difficulty or intellectual disability (ID), usually mild to moderate, has been recorded. Difficulties around focussing on carrying out tasks were mentioned by a number of *Unique* parents.

There isn't much detailed information relating to schooling, but among *Unique* members many attended a mainstream (public) school, where necessary with 1:1 help or dedicated support workers for specific areas of concern. For a child with a more severe LD, 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. The experience of obtaining appropriate support varied considerably among *Unique* members (*see* below).

Playing word and number games, such as dominoes, can aid learning

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

“ He had average levels of literacy and numeracy at nine years, but lacked concentration and focus and had difficulties with motivation. He struggled at school due to lack of support and understanding of his disorder and its consequences.

As my son has got older it is becoming very clear what he can and cannot do. His communication difficulties and comprehension have also led to him being significantly behind in all his learning and he has extreme aversion to learning anything new due to fear of failing and of injuring himself. Now, aged 12,

he is steering his own learning in the direction he wants to go. He better understands his abilities and will participate more when he enjoys the learning. He is extremely hands on and prefers to learn through doing rather than listening and making notes; he is more interested if he can see someone demonstrate a skill and then copy it. We believe he has dyslexia, which is being investigated. He is more able in some areas such as numbers, maths, puzzles, science and art. These things make sense to him since rules apply.

We are currently in the appeal phase to issue an EHC plan. The process has been the hardest thing I have ever done. The struggle to try and prove that your child needs support is awful. Currently, my son attends a mainstream school. It is an academy which means that they have more free rein when it comes to the kind of support they provide; however, it is becoming clear that the school can only provide support to a small degree. Having a good relationship with the school SENCO is important. Really, my son should attend a specialist unit which deals with autistic students; however, these places are extremely limited and to get a placement in a specialist school can take years. I would thoroughly recommend parents start the EHCP process as soon as possible.” - del 15q25.2q25.3 mat, 12 years, UK

“At three years, she is soon going to start at nursery part-time and is due to attend a special education school from five-and-a half years. I'm sure she will enjoy it as she loves being around other children and adults.” - del 15q25.2, 3 years, UK

“He has mild intellectual disability. He has been successful in school with a very detailed IEP, which was not a problem to obtain, but has a very hard time focusing and has a low tolerance for frustration. He attended public [state] school. My advice it to know your rights and stay involved.” - del 15q25.2q25.3, 19 years, US

“He has a low IQ, but since his adaptive functioning is higher [an individual's ability to achieve age-appropriate maturity, judgment and reasoning; social sensibility; and personal independence], he's not currently diagnosed as having intellectual disability. Reading is age/grade appropriate, but reading comprehension is delayed by three to four years. He currently attends public [state] school, but has been in a special education classroom since first grade. He is in mainstream classes for Gym, Art, Music, Science (with modified curriculum and support). My advice would be to work with an IEP advocate who can help you navigate the process and ensure your child gets the services they need. Make sure you follow their programme, progress and goal-mastery closely.” - del 15q25.2q25.3, 13 years, US

Speech and Communication

The information we have from *Unique* members and medical literature suggests that speech is typically one of the most commonly affected areas of development. In the 2020 survey, all but one parent mentioned speech delay to some degree. Parents often felt that their child's comprehension of language (receptive language) was significantly better than their ability to communicate using language (expressive language). Difficulties with articulation, which make it difficult to make clearly intelligible speech sounds and can make communication with strangers a challenge, was referred to by many parents (5/7 in *Unique* survey) and often persisted. With time, it appears that older children tended to use long, complex sentences.

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 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 affected by RCDs, including 15q25 deletions. Any concerns around hearing should also be acted on early to help reduce any impact on speech.

"She has speech delay. Has good receptive language skills and can understand instructions. She communicates in her own way using baby language and gestures and is able to mimic others. At two-and-a-half years, she would say words like "baba" for "daddy" and "bath" - words beginning with "b". She enjoys "talking" using her toy telephone. At three years, her vocabulary is increasing and she is having speech and language therapy." - del 15q25.2

"My children [with the same inherited 15q25 deletion] all use a combination of PECS, communication cards (at school) and Makaton. They can speak when comfortable and their anxiety is low and use complex and often grown up sentences like an adult.

My 12-year-old child is the most affected by selective (situational) mutism and will go days without speaking. He started to speak aged three at home but not until he was five outside of the home. He can speak in a situation where he is comfortable and will chat for hours, but these comfortable situations are becoming less and less frequent. He prefers his own company more and more. He mainly uses gestures, communication cards and PECS. Currently trying to put SALT in place." - del 15q25.2q25.3 mat, 12 years

“ He started to speak closer to three years. His speech is normal in terms of sentences, but he talks fast and has to stop and slow down to speak more clearly. His expressive speech has always been a problem, especially in school. ” - del 15q25.2q25.3, 19 years

“ Delayed in attainment of language, speaking first words at three years and combining words at four years. Speech therapy started at three years. The “r” sound is most challenging. Uses long, but not complex, sentences. Speech articulation issues make it difficult to understand him and he also tends to speak too fast. He has difficulty understanding and expressing age/grade appropriate material. ” - del 15q25.2q25.3, 13 years

“ He understands more than he can express by quite a large margin, according to his most recent speech evaluation. He communicates using individual words, sounds, gestures, sign language, PECS and an AAC device (touch chat). ” - del 15q25.2, 3.5 years

“ She understands everything but has problems expressing herself. ” - del 15q25.2, 3 years

Personality

It is important to remember that every child is an individual and not all personality traits will be related to the chromosome disorder. The testimony we have from *Unique* families speaks to children who are kind, thoughtful, funny, caring individuals. There appears to be a tendency for children to find social interactions challenging and they may be somewhat anxious and shy around strangers or in new social situations, but once comfortable they come out of themselves. Children could also experience sudden mood swings. In common with their peers, many children enjoyed being active and relished a range of activities, including playing tennis, Lego, video games, running, ice hockey and drawing.

“ To a stranger, he might seem quiet, withdrawn, or anxious. Once he is familiar with you, he communicates fine. He loves to laugh and tell jokes. He is tender-hearted and tries to be helpful. ” - del 15q25.2q25.3, 19 years

“ He is an extremely kind child. He hates to disappoint or upset people and is caring and considerate; however, he also is quite rigid in his thinking, which can cause some upset among those who don't understand this. He is passionate about what he likes and dislikes. He struggles to start conversations and understand social cues and rules. ” - del 15q25.2q25.3 mat, 12 years

“ Likes to be social, but can be shy at times. He is a very thoughtful and loving child and has a good sense of humour. Likes to be active and play sports. ” - del 15q25.2q25.3, 13 years

Social, emotional & anxiety disorders

The 15q25.2 region of chromosome 15 has been linked to an increased risk of developing neurodevelopmental and neuropsychiatric disorders, with some suggestion that deletions involving the more distal region may be more susceptible to these than those involving the proximal region alone. These disorders can have an impact on the development of motor skills, learning and speech, but also include social, emotional and anxiety disorders, such as autism spectrum disorder (ASD); anxiety, attention deficit hyperactivity disorder (ADHD); sensory processing disorder (SPD); schizophrenia; obsessive compulsive disorder (OCD); and seizures.

A diagnosis of one or more social, emotional or anxiety disorder (*see* Types of social, emotional and anxiety disorders, pg 21), including ASD, ADHD and SPD, was reported by at least eight *Unique* families. Some children had shown features of these disorders but had not received an official diagnosis. In medical literature, several cases of autism, seizures and two cases of mental health problems have been described. A 9-year-old girl with a 15q25.2 deletion exhibited autistic features in addition to other distinctive behaviours including hyperactivity, attention deficits and oppositional behaviour (Itsara 2009; Cooper 2011; Palumbo 2012; Doelken 2013; Burgess & Brown 2014; DECIPHER; Unique).

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 then to a behavioural or clinical psychologist to undergo assessment. There is not a 'medical test' that can diagnose autism, 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 has behavioural and sensory problems, including ASD, ADHD, OCD,

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.

ODD and severe anxiety. On a bad day, he is angry and shouty and will spend most of the day in the specialist unit at school. Anything can cause a bad day e.g. a change of teacher, routine, even meal can upset him. On a good day, he will use music to drown out noises that upset him; he finds music therapeutic and he works better when wearing headphones. He will travel through each lesson at school without much understanding of what is happening, but happy in his own space. ” - del 15q25.2q25.3 mat, 12 years

“ As a small child, he picked his nose a lot, and smeared his faeces sometimes. He also scratched himself. On starting school at five years there was immediate concern over his behaviours and he was found to have many traits of autism; he communicated effectively but preferred playing alone and hated noise. He has a low tolerance for frustration. He shuts down rather than having a tantrum but will not move until he is ready. He is a creature of habit and has been called a human GPS, knowing exactly how to get to a place if he has been there once. ” - del 15q25.2q25.3, 19 years

“ He has not been diagnosed with SPD but doesn’t like certain textures. On a good day, he’s very attentive, willing to try new things, has a lot of energy. On bad days, he doesn’t listen well and demonstrates oppositional defiance. ” - del 15q25.2, 3.5 years

Sleep

Several parents told us that their child had experienced issues around sleep. These included difficulty ‘switching off’ at night, not sleeping for long periods of time and waking repeatedly in the night. Reasons for sleeping difficulties are not always well understood and are also experienced by many typically-developing children (Unique).

Where sleep has been particularly challenging, some *Unique* families with a child(ren) affected by a rare chromosome disorder, including those with a 15q25 deletion, have favoured the use of prescribed medicines, including antihistamines with a sedating effect or the naturally-occurring hormone melatonin, which can help synchronise the body clock. These treatments should only be undertaken after consultation with a medical professional.

One child with a 15q25.2 deletion had severe obstructive sleep apnoea (OSA), where normal breathing is disrupted during sleep. He required continuous positive airway pressure (CPAP) during the night (Burgess & Brown 2014).

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

Since many of the individuals we know about with a 15q25 deletion are babies

or younger children, there is only extremely limited information available relating to puberty. We do know that three *Unique* boys went through puberty at the expected age, or possibly a little early, and the process was unremarkable.

For girls, puberty appears to be delayed in some case, and a link between 15q25.2 deletions and primary ovarian insufficiency (POI) (also known as premature ovarian failure (POF)) has been suggested (*see* Primary ovarian insufficiency (POI), pg 26).

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

Medical concerns

General well being

Unique families often described their child's general state of health as "generally healthy". However, some parents did tell us that their child had been susceptible to colds and other respiratory infections in baby– and early childhood. A few children have on-going health concerns, including feeding difficulties, anaemia and asthma (Unique).

"She suffered from double pneumonia and dehydration shortly after she turned one-year-old and has always been very susceptible to upper respiratory infections." - del 15q25.2

Anomalies of the chest, spine & abdomen

Anomalies of the chest and abdomen are one of the more common features associated with 15q25 deletions. Although relatively uncommon, a congenital diaphragmatic hernia (CDH) was seen in at least six babies with a 15q25.2 deletion, including two *Unique* babies. A CDH occurs when the diaphragm that separates the contents of the abdomen from those of the chest cavity, does not develop properly. When this happens, the contents of the stomach may protrude into the chest cavity, preventing the lungs from developing properly. Additionally, at least three babies with a 15q25.2 deletion had an inguinal hernia (where part of the small intestine protrudes through the groin area at the top of the inner thigh) and one an umbilical hernia (where part of the small intestine protrudes through the abdominal wall near the belly button). At least four children had pectus excavatum (a sunken chest), in two cases associated with CDH. Three of these children, one with CDH, also had scoliosis, where there is a sideways curve of the spine. A boy also had scoliosis, apparently without pectus excavatum, and a girl had kyphosis, where there is an outward curve of the spine, and delayed bone maturation.

There are various degrees and types of diaphragmatic hernia. Depending on the type and severity, it may be detectable on routine prenatal ultrasound scans or may not be detected until after birth. A baby born with a large

diaphragmatic hernia will usually need respiratory support or ventilation at birth, while surgical repair of the hernia will allow the lungs space to develop. Techniques and outcomes of surgery continue to improve and there are several cases involving 15q25.2 deletions where surgery has been successful. Repair of small or partial hernias is generally more straightforward. More information on CDH can be found at the registered charity CDH UK (https://cdhuk.org.uk/) (Wat 2010; Doelken 2013; Burgess & Brown 2014; DECIPHER; Unique).

“Diagnosed prenatally at 16 weeks a CDH and was operated on soon after birth. This meant she was tube-fed and needed to spend 10 weeks in intensive care and was on a ventilator for 8 weeks. Her doctors said that her diagnosis with a 15q25 deletion meant she shouldn't undergo Fetoscopic Endoluminal Tracheal Occlusion (FETO) or be placed on an Extracorporeal Membrane Oxygenation (ECMO) machine. Needed a revision at 12 months as three stitches in the diaphragm had come undone.

Her health now is generally fine, and there have been no further problems since the correction, but her left lung isn't properly formed due to the CDH. She is on long-term preventative treatment for respiratory infections since she is at increased risk, especially during the winter. She also has scoliosis and a sunken chest and has been given a back brace.” - del 15q25.2, 3 years

Anaemia

Anaemia is one of the more common features associated with 15q25.2 deletions. Anaemia occurs when there are too few red blood cells (RBCs) in the blood or the concentration of haemoglobin (the protein molecule in RBCs that carries oxygen) in the blood is too low, meaning the amount of oxygen that your blood can carry to the body's tissues is reduced. Anaemia leads to variable symptoms, including fatigue, shortness of breath, dizziness/light-headedness and an irregular heartbeat and can take a number of different forms with multiple possible causes.

Some children with a 15q25.2 deletion have been diagnosed with macrocytic anaemia (where the RBCs are abnormally large), iron deficiency anaemia or anaemia that was presumed to have been caused by another long-term condition. Other children, including at least three *Unique* members, were found to have anaemia caused by erythroid hypoplasia, where an abnormally low number of RBCs are produced and released into the bloodstream by the bone marrow. This type of anaemia is seen in people with a condition called Diamond–Blackfan anaemia (DBA). DBA is a rare blood condition characterised by failure of the bone marrow to produce enough RBCs and often also macrocytic anaemia, as well as other health and developmental problems. There are many different genes known to cause DBA. One cause of DBA is deletion of the *RPS17L* gene located in 15q25.2 (*see* Genes, pg 31). The high incidence of anaemia in individuals with 15q25 deletions has led some to suggest that patients with deletions including the proximal region of

15q25.2 should be routinely screened for anaemia, with regular blood tests.

Once diagnosed, anaemia can usually be treated effectively. Individually, a 10 -week-old boy diagnosed with DBA responded well to blood transfusion and the administration of oral steroids, while a girl with iron deficiency anaemia - diagnosed soon after birth - responded well to treatment with iron supplements (Wagenstaller 2007; Wat 2010; Doelken 2013; Burgess & Brown 2014; DECIPHER; Unique).

"He has regular occurrences of supraventricular tachycardia (SVT). He suffered his first SVT at about six months old. Was in ICU for a week and then transferred to an isolation ward for fear of hidden infection. Eventually diagnosed with pneumonia and no further investigation into SVT was done. Currently investigating DBA as a result of numerous SVT attacks, and fainting spells" - del 15q25.2q25.3 mat, 12 years

"Has Diamond-Blackfan anaemia. Blood transfusion and tests when needed." - del 15q25.2

Thrombosis

At least five individuals with a 15q25.2 deletion, including one *Unique* member, were diagnosed with portal vein thrombosis (PVT), although the exact cause in these cases was not known. PVT occurs when a blood clot causes a narrowing or blockage of the vein that carries blood from the intestines to the liver. Often there are no symptoms, but in some cases PVT can lead to liver problems, which can cause an accumulation of fluid in the abdomen (ascites), an enlarged spleen and/or severe bleeding in the oesophagus (the tube that carries food from the mouth to the stomach), which can lead to anaemia. At least four also experienced chronic anaemia (*see* above).

Cases included a seven-year-old boy, who had previously undergone bypass surgery for PVT, and experienced bleeding in the oesophagus for which he required blood transfusions. At 17 years, he experienced occult gastrointestinal varicosis bleeding which resulted in iron deficiency anaemia. An 11-year-old girl developed portal vein stenosis with bleeding from enlarged veins in the oesophagus (oesophageal varices), which could have been caused by PVT (Wagenstallar 2007; Doelken 2013; Burgess & Brown 2014).

Anomalies of the kidneys

Anomalies of the kidneys have been found in a small number of babies. Where treatment is necessary, this will depend on the nature of the disorder. A baby boy with a 15q25.2 deletion had small cysts on his kidneys that resolved without treatment, while a baby girl with a similar deletion had very small kidneys. Her right kidney was also located in the pelvic area instead of in the usual position higher up in the abdomen. DECIPHER also lists an

unspecified abnormality of the upper urinary tract (Wat 2010; Burgess & Brown 2014; DECIPHER)

Anomalies of the genitals

Minor anomalies of the genitals are common in children with a chromosome disorder. It seems that perhaps half of boys with a 15q25.2 deletion had undescended testicles at birth (cryptorchidism). In a significant number of boys without any chromosome abnormality, the undescended teste moves 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). One boy had a hydrocele (an accumulation of watery fluid in a sac around the testes), which may require draining. A boy also had a small (micro) penis that was buried (hidden) (Wat 2010; Burgess & Brown 2014; Unique).

Primary ovarian insufficiency (POI)

Although data is limited, a link between 15q25.2 deletions and primary ovarian insufficiency (POI) (also known as premature ovarian failure (POF)) has been suggested in medical literature. POI is characterised by the early loss of the normal function of the ovaries before the age of 40 and causes early menopause. At least five girls in medical literature had not started their periods within the expected age range (primary amenorrhea), a situation that should alert doctors to investigate ovarian function. In these cases, POI was established to be the cause of primary amenorrhea. It is estimated that about 1% of all women with POI are thought to have a 15q25.2 deletion. If you have any concerns, you should speak to your child's doctor/ health care provider. The *BNC1* gene in 15q25.2 has been linked to POI (OMIM # 618723) (McGuire 2011; Hyon 2016; Chen 2020; DECIPHER).

Heart conditions

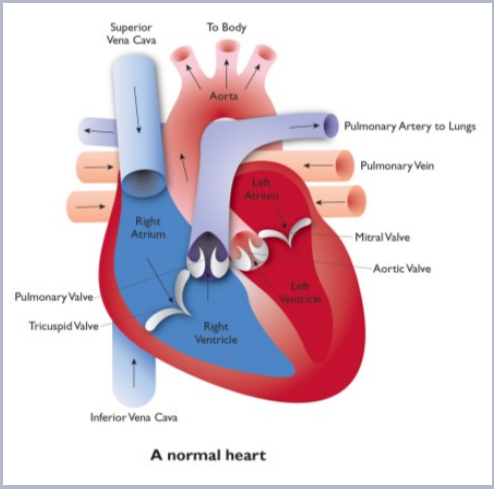
A range of heart conditions (*see* Heart Conditions box, pg 27) have been reported, affecting at least nine babies in medical literature and six *Unique* babies. Many of these conditions were minor and/or resolved naturally without any need for treatment or surgery. A few babies had more than one condition.

In medical literature, reports included a five-year-old boy whose heart was positioned to the right instead of left of the chest (dextrocardia), but which was otherwise structurally normal. Two babies had a ventricular septal defect (VSD), where there is one or more holes in the wall between the two pumping chambers of the heart (ventricles). While small VSDs may close spontaneously, a larger VSD usually needs surgical repair to prevent lung problems that would develop from extra blood flow. One baby also had an atrial septal defect (ASD), where there is a hole between the upper chambers of the heart. Both the VSD and ASD were successfully correct by

Heart conditions

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.



A normal heart

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.

surgery. A further two babies also had an ASD. A baby boy had a coronary artery fistula, where there is an abnormal connection between the blood vessels which carry blood to the heart from the lungs and a chamber of the heart or another blood vessel. The connection may need to be corrected surgically. The details of heart conditions affecting *Unique* members are outlined below (Wat 2010; Cooper 2011; Burgess & Brown 2014; Chen 2020; DECIPHER; Unique).

“ She had a heart murmur that we later found was permanent and due to an aortic stenosis. She had open heart surgery at six years and will need more surgeries in the future. ” - del 15q25.2

“ Congenital VSD repaired and valvuloplasty at four years. At 14 years he still has a murmur and some aortic insufficiency. ” - del 15q25.2q25.3, 19 years

“ Congenital pulmonary stenosis which self-corrected by six months. ” - del 15q25.2q25.3

“ Congenital coarctation, VSD, PFO, LVCS. ” - del 15q25.2q25.3

“ Heart defect that has now closed at seven years. ” - del 15q25.1q26.1

Head shape & brain anomalies

A few babies with a 15q25 deletion are born with a head that is an unusual size or shape. Several had an unusually small (microcephaly) or large (macrocephaly) head. One *Unique* baby had plagiocephaly, where baby's head is flat on one side, and one had a "tower-like" head shape (oxycephaly/turricephaly).

Most babies with 15q25.2 deletion had no anomalies of the brain. There are a few individual cases reported, including a baby boy with a 2.5 Mb 15q25.2 deletion who had a small corpus callosum (the band of nerve fibres joining the left and right sides of the brain) and another with cerebellar vermis hypoplasia (part of the brain - the cerebellar vermis - is smaller than usual or underdeveloped), but these cases appear to be very much the exception (Wat 2010; Burgess & Brown 2014; DECIPHER; Unique).

Hands & feet

Some parents may notice unusual features of the hands and feet. Those we know about include a single palm crease on the hands; short fingers/toes; unusually long fingers/toes; curved fingers; mallet toe; “puffy” feet; thin (hypoplastic) nails; and sandal gap (Palumbo 2012; Doelken; Burgess & Brown 2014; DECIPHER; Unique).

“ He has a curling in little finger and excessive flexibility in the finger joints, leading to poor handwriting and fine motor skills. ” - del 15q25.2q25.3 mat

Eyes & Vision

Occasionally, *Unique* parents told us about minor anomalies of the eyes or vision. Two children were short-sighted (myopia) and one was long-sighted (hyperopia). One *Unique* member and one baby in medical literature had astigmatism, leading to blurred vision. Where necessary, individuals may benefit from wearing glasses.

Two *Unique* members had a squint (strabismus), where one eye or both turns inward, outward, up or down. Strabismus 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 strabismus may only be corrected following a surgical operation. At least one child developed a "lazy eye" (amblyopia), which can be a consequence of a constant squint in one eye. One child had a confirmed defect of the retina (Burgess & Brown 2014; Unique).

Hearing

Hearing appears to be generally unaffected, but a few children experienced some degree of hearing loss. Some children are also particularly prone to ear infections, which can be very painful and debilitating. 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. Where the hearing loss is permanent, hearing aids or assisted listening devices may help as a temporary or longer-lasting measure. Treatment of ear infections with antibiotics and/or grommets may be necessary. One child had intermittent tinnitus, where the sufferer hears a noise, such as ringing, hissing or buzzing, that is not caused by an outside source (Burgess & Brown 2014; Unique).

"She has always been very susceptible to earache. She was born with perfect hearing, but around age seven-nine she lost her hearing completely in the left ear and has very weak hearing in the right ear. At 11 years she receives audiology services at school (uses FM system [an FM system uses radio waves to deliver speech signals directly from the speaker's mouth to the listener's ears])." - del 15q25.2

"Failed a hearing test at school but later passed at his doctor's office." - del 15q25.2q25.3

"Chronic ear infections. Grommets." - del 15q25.2q25.3

"Multiple hearing tests which found a slight hearing loss unilaterally. To be rechecked at one year." - del 15q25

"No concerns about hearing." - del 15q25

Limbs & Joints

Joint hypermobility (laxity) affected several *Unique* children and means that babies and children can move their limbs into positions others find impossible. While this may cause no problems, hypermobility is sometimes associated with pain and stiffness in the joints and muscles, joints that dislocate (come out of position) easily, and injuries including sprains. It can also affect fine and gross motor skills. One *Unique* child dislocated a knee (Unique).

Teeth

Dental problems are very common in children with a chromosome disorder and a high standard of dental care is important to minimise damage by decay and erosion. Dental concerns have occasionally been reported among children with a 15q25 deletion, including delayed tooth eruption, tooth grinding (bruxism), abnormally thin and weak enamel (enamel hypoplasia), gaps between the teeth, and overcrowding (Palumbo 2012; Unique).

"His teeth have a rough texture and tartar build-up is a problem. He has to have them cleaned at the dentist every three months, but he has no cavities. He also had gum tissue implanted in the lower jaw due to receding." - del 15q25.2q25.3, 19 years

"He had a gap between his top front teeth, but the rest of his teeth were crowded, which required extractions. He wears braces currently." - del 15q25.2q25.3, 13 years

Palate

Very rarely, babies were born with an anomaly of the palate, with individual cases of a high-arched palate, a cleft palate and a cleft lip recorded. Anomalies of the palate, particularly clefting, can cause difficulties in feeding, hearing, teething and speech production. As well as helping aesthetically, surgical repair may ease these problems and may even eliminate them altogether (Wat 2010; Burgess & Brown 2014; Unique).

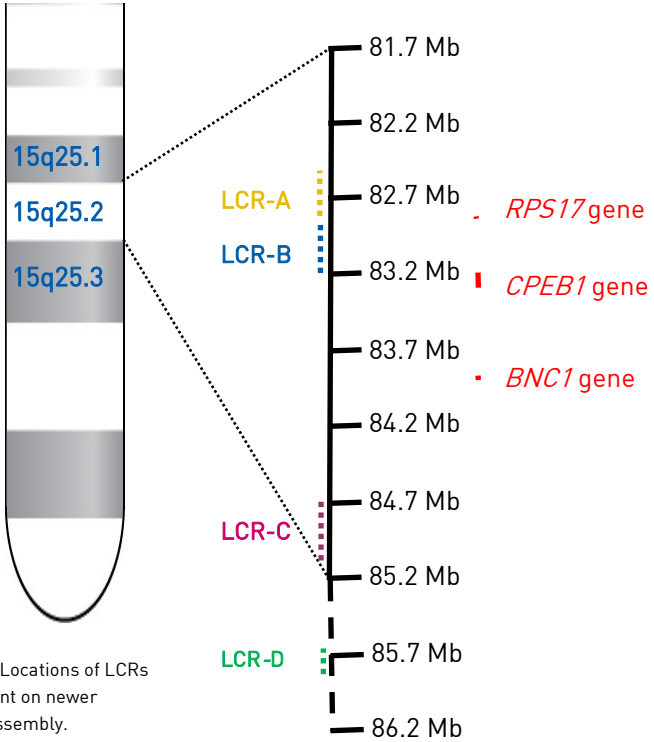
"High arched palate. Has required speech therapy since age three. Still has speech articulation issues." - del 15q25.2q25.3, 13 years

Other medical concerns (*Unique* members)

Cortisol deficiency: one case
High thyroid-stimulating hormone (TSH) levels: one case
Excessive hair growth: two cases
Eczema: three cases
Low platelet count: one case
Café-au-lait (CAL) spots: one case
Acne: one case

Genes

An individual 15q25 deletion will include a particular set of genes and other important regulatory sequences that control 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 15q25 deletions. The possible role of a few genes within 15q25 that are included in known deletions include:



Based on GrCh37/Hg19. Locations of LCRs and genes will be different on newer GrCh38/Hg38 genome assembly.

RPS17 (Ribosomal Protein S17)

also known as: S17; DBA4; RPS17L; RPS17L1; RPS17L2

Location: 15q25.2

[82,536,750 - 82,540,457 (GRCh38/hg38) (from NCBI - Nov 2020)]
[82,821,161 - 82,824,865 (GRCh37/hg19) (from NCBI)]

Usually, the *RPS17* gene exists in two copies, one on each chromosome 15. When one copy of *RPS17* is faulty or deleted, this causes a condition known

as Diamond Blackfan Anaemia (DBA). It has been suggested that the loss of one copy of *RPS17* could be responsible for the anaemia and other red blood cell problems that are frequently seen in many individuals with proximal 15q25.2 deletions (Wat 2010; Burgess & Brown 2014; Ulirsch 2018; Chen 2020).

BNC1 (Basonuclin 1)

also known as: BNC; BSN1; POF16; HsT19447

Location: 15q25.2

[83,255,884 - 83,284,664 (GRCh38/hg38) (from NCBI)]
[83,924,655 - 83,953,468 (GRCh37/hg19) (from NCBI)]

The *BNC1* gene is thought to be an important candidate gene for primary ovarian insufficiency (POI) (*see* pg 26). One cause of POI is thought to be loss (or haploinsufficiency) of one copy of the *BNC1* gene. One large family, in which six women had POI, showed a tiny deletion involving part of *BCN1* (Zhang et al 2018). Men with this deletion had no fertility problems. When one copy of the *BCN1* gene is deleted, this means too little of the BCN1 protein is produced to maintain normal function. The *BCN1* gene is highly expressed in the ovary, and it possibly plays a role in regulating the expression of other genes in the body (Hyon 2016; Zhang 2018; Chen 2020).

CPEB (Cytoplasmic Polyadenylation Element Binding Protein 1)

also known as: CPE-Binding Protein 1; CPE-BP1; HCPEB-1; H-CPEB; CPEB; Cytoplasmic Polyadenylation Element-Binding Protein 1; CPEB-1

Location: 15q25.2

[82,543,201 - 82,648,795 (GRCh38/hg38) (from NCBI)]
[83,211,948 - 83,316,762 (GRCh37/hg19) (from NCBI)]

The *CPEB1* gene is highly expressed in the brain. Deletion of *CPEB1* is thought to be one of the causes of the neurodevelopmental features associated with 15q25.2 deletions. In support of this, a girl with a 15q25.2 deletion not including *CPEB1* did not have developmental delay or intellectual disability (Chen 2020). However, it is not clear, based on current evidence, if the *CPEB1* gene is actually the cause of the neurodevelopmental features seen in some individuals with 15q25.2 deletion.

The *CPEB1* gene is also involved in the development and maturation of eggs (oocytes). One study (Hyon 2016) suggested that deletion of the *CPEB1* gene could be responsible for premature ovarian failure seen in some females with 15q25.2 deletion. However, the three individuals they identified with deletions of 15q25.2 and ovarian insufficiency were also missing the *BNC1* gene. It is possible that both *CPEB1* and *BNC1* could be contributing in some way to ovarian function.

Families say...

❝ You must take the initiative and seek help - don't be afraid to do so. Special Olympics has been a great help with socialisation and forming a parental network. Take time for yourself and for your partner. Know that you have this special child for a reason, and that there are gifts in them you may not know yet. There is no one to blame for their condition, but embrace them and love them and reach out for help. Write down questions so when you visit the doctor, developmental paediatrician etc., you will remember them.❞

❝ She has a brother who's her hero. He's always checking if she's OK. But he feels sometimes alone, not in his place, and not our priority. We try to show him he is, too. Earlier, it was way more difficult because we had to adjust our jobs and planning for her, but now, fingers crossed, life is a bit easier.❞

❝ She is a happy little girl no matter what. She is really good with her siblings and loves to play. I wouldn't change her for the world! ❞

Websites

https://patient.info - information on medical conditions and terms

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

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

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

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

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

This booklet was first compiled by Unique (CA) in 2020 and reviewed by Associate Professor Sue White (Clinical Geneticist) & Dr Natasha Brown (Clinical Geneticist), Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Victoria 3052, Australia.
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