Understanding Chromosome & Gene Disorders

15q14 deletions

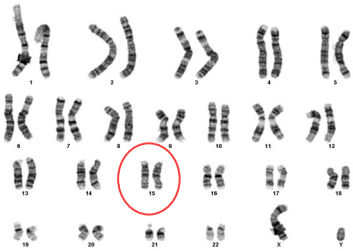
rarechromo.org

15q14 deletions

A chromosome 15q14 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 15q14 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.



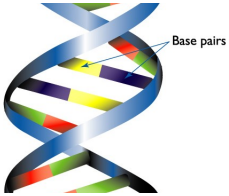
Chromosome pairs 1-22, X and Y (male). Chromosome 15 pair circled in red

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

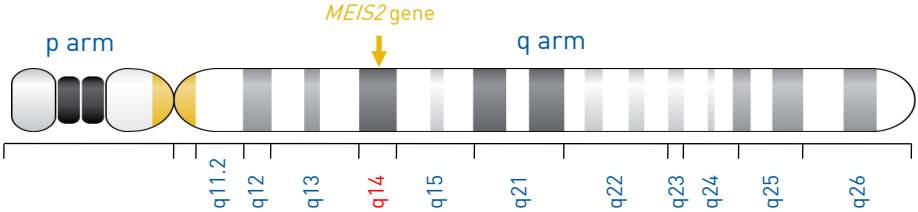
Each chromosome contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. There are millions of base pairs in every chromosome, and they are often counted in millions, where 1 Mb equals one million base pairs. The whole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

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 15q14 deletion have one unaffected chromosome 15, but the other chromosome 15 has chromosomal material missing from all or part of band 15q14 on the long arm (marked in red). Some people also have larger deletions that extend into other bands e.g. 15q12, 15q13, 15q15.

The 15q14 band contains a gene called *MEIS2* (*see* pg 4). Although cases are rare, complete or partial loss (deletion) of *MEIS2* has been shown to be responsible for the major features of a novel 15q14 deletion syndrome that has been described in medical literature (OMIM #616898). Changes (mutations) to *MEIS2* that mean that one copy does not function normally, can also be associated with these features (Shimojima 2017; Verheije 2019).

The majority of 15q14 deletions that we know about include the complete or partial deletion of the *MEIS2* gene, but in a few cases the 15q14 deletion does not involve *MEIS2*. Other genes are usually also deleted and can also play a role in the features observed.

Sources

The information in this booklet is drawn from the 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. Three *Unique* members completed a detailed survey in 2020. In addition to this, information has also been drawn from the database records of other members where possible.

The *MEIS2* gene

Location: 15q14

37,183,222 - 37,393,500 (GRCh37/hg19) (from NCBI)

36,889,204 - 37,101,311 (GRCh38/hg38) (from NCBI)

The *MEIS2* (Meis Homeobox 2) gene codes for a protein that helps control the expression of other genes and has been shown to play a role in controlling the growth of the developing embryo during pregnancy. It has been suggested that having a missing copy of *MEIS2*, or other mechanisms that lead to under-expression of the gene, may contribute to the features associated with 15q14 deletions, including anomalies of the palate, characteristic facial features, congenital heart defects and autism spectrum disorder (ASD) (Roberti 2011; Johansson 2014; Shimojima 2017; Douglas 2018; Verheije 2019).

Chromosomal changes

When a sperm and egg cell join they 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 deleted, duplicated and/or become rearranged. Since the breakpoints of the deleted region for 15q14 deletion vary from person to person, it has been suggested that deletions arise when a mistake occurs during a process called non-homologous end-joining, which is involved in repairing breaks in the DNA molecule (Verheije 2019).

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 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 15q14, are called microdeletions. Many people who have a microdeletion may 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 only be offered if there is 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/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. In this case, cells containing a 15q14 deletion could exist alongside cells with a "normal" chromosome number and arrangement. We know about several cases of 15q14 deletion mosaicism: one *Unique* member, and a boy with a tiny 123 kb deletion that included part of the *MEIS2* gene and was thought to be present in about 40% (4 in 10) of cells, but not in the remaining 60% (6 in 10) of cells (Crowley 2010; Unique).

The proportion of cells with the 15q14 deletion in the different tissue types that make up the body can vary, which will influence the outcome. The 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 rare but where it has been reported in medical literature for other rare chromosome disorders, the outcome of the condition 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 including 15q14 might have results that look like one of these examples:

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.

The databases commonly used by clinical geneticists and *Unique* will soon move to a more recent assembly named GRCh38/hg38, which was released in 2013. Genetic reports will at some point also be altered, so genes and genetic changes may have new base pair numbers.

46,XY,del(15)(q14q15.1) - 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. (q14q15.1) shows the part of the chromosome that is deleted; in this case, there is a loss of a chromosome segment involving bands q14 and q15.1.

arr[hg19] 15q14(35213690_39041011)x1 dn This result shows that the analysis used microarray technology (arr). The analysis revealed a DNA anomaly involving 15q14. 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 35213690 and 39041011 (by taking the first number from the second, you can work out that this is 3,827,321 base pairs, or 3.8 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(15)(q14)[18]/46,XX,[12] This is 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. Eighteen ([18]) cells had a deletion of chromosome 15 (del

(15)). (q14) shows the part of the chromosome that is deleted; in this case, there is a loss of a chromosome segment from q14. Twelve [12] cells showed a normal karyotype for a girl or woman (46,XX).

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 15q14 deletions?

It is difficult to estimate the prevalence of 15q14 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, at least 30 cases of a deletion involving 15q14 alone as their sole genetic anomaly have been reported in medical literature, and *Unique* had a further six members. Ages ranged from babies to a 33-year-old adult and almost all the deletions included complete or partial deletion of the *MEIS2* gene.

Some people have deletions involving 15q14 but which extend into other bands e.g. 15q12, 15q13, 15q15, including several *Unique* members. Others have a more complex karyotype, where in addition to a 15q14 deletions they also had recorded genomic variants involving another chromosome(s) e.g. other deletions or duplications (Erdogan 2007; Chen 2008; Brunetti-Pierri 2008; Crowley 2010; Johansson 2014; Shimojima 2017; Chen 2016; Gambin 2017; Verheije 2019; DECIPHER; Unique).

Note: 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 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.

15q14 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 15q14 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 found to have "normal" chromosomes, it is very unlikely that another child will be born with a 15q14 deletion or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry 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 duplication.

In families where the 15q14 deletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 15q14 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 15q14 deletion goes on to have children of their own, the chances of passing on the deletion to their child are 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.

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 a 15q14 deletion often occur in this way in a condition known as 15q14 (micro)deletion syndrome.

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 15q14 deletion is unique and the developmental and medical concerns they experience will vary.

However, the most common features associated with 15q14 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.

Features associated with 15q14 deletions:

- Some degree of developmental delay
- Some degree of intellectual disability
- Speech delay/difficulties with speech
- Anomalies of the palate e.g. cleft palate, bifid uvula, a high/arched palate
- Low muscle tone (hypotonia)
- Joint hypermobility (laxity)
- Feeding difficulties
- Heart anomalies
- Characteristic facial features
- A small head (microcephaly)
- Short stature
- Undescended testes at birth in boys (cryptorchidism)
- Café-au-lait spots (CALs)
- Social, emotional and anxiety disorders
- Frequent ear infections/glue ear, which usually resolve during childhood
- Minor anomalies of the hands and feet
- Minor dental concerns

(Erdogan 2007; Brunetti-Pierri 2008; Chen 2008; Roberti 2011; Johansson 2014; Chen 2016; Verheije 2019; DECIPHER; Unique)

Expanded Prader-Willi Syndrome

A child who has lost material from the proximal part of the long arm of chromosome 15 between 15q11 and 15q13, including a segment of the chromosome known as the PWACR (the Prader-Willi and Angelman Critical Region (PWACR)), is liable to develop one of two well-known syndromes. If the deletion has arisen on the chromosome 15 that came from the father, as is the case in approximately 70% of cases (Calounova 2008), the child will have Prader-Willi syndrome, characterised by being overweight and of below average height; overeating; small genitalia in boys and men; low muscle tone (hyoptonia) and dysfunction of the central nervous system. If the deletion has arisen on the chromosome 15 that came from the mother, the child will have Angelman syndrome (AS), characterised by developmental delay; speech delay or no speech; a movement and balance disorder; an excitable personality and inappropriately happy disposition. PWS and AS occurs in approximately 1 in 22,000 – 25,000 live births (Whittington 2007).

Subsequently, an Expanded Prader-Willi Syndrome has been described in

medical literature. Patients with Expanded PWS have the usual characteristics of PWS, but these characteristics may be more severe in nature or include other features that are not seen in classic cases of PWS (Liu 2013; Xefteris 2019). Children with Expanded PWS typically have a deletion that includes the PWACR but also encompasses other regions of chromosome 15q, including 15q14.

A girl with a *de novo* deletion of chromosome 15q11-q14 that included the PWACR but extended in to band 15q14, had features including hypotonia and feeding problems that are typical of PWS. In addition, she had features including congenital heart disease, speech delay and swollen feet that are not typically observed in PWS but which have been observed in those with 15q14 deletions (Butler 2010).

A number of other cases of expanded PWS have been reported with 15q deletions that include regions outside the PWACR, with additional case-specific features including microcephaly, anomalies of the palate, absence of speech and heart conditions, in addition to those typically associated with PWS.

Crucially, where a child with PWS has more severe or additional features, doctors should carry out further genetic testing to determine the exact nature of the deletion(s) and genes involved and undertake additional medical tests, such as an echocardiogram (ECG) of the heart, which will help provide more accurate counselling to parents (Liu 2013; Xefteris 2019).

This leaflet does not cover these syndromes but more information for UK families can be found at:

Prader-Willi Syndrome Association UK **www.pwsa.co.uk** 01332 365676
Suite 4.4 Litchurch Plaza, Litchurch Lane, Derby, DE24 8AA UK

Angelman Syndrome Support Education and Research Trust ASSERT
www.angelmanuk.org 0300 999 0102 PO Box 4962, Nuneaton, CV11 9FD, UK

Diagnosis

The majority of *Unique* members received a diagnosis at or soon after birth or within the first few years of life, usually as the result of a delay in reaching developmental milestones or health concerns. Early diagnosis can enable appropriate support and interventions to be put in place (Unique).

“ She was first tested after an abnormality was detected by 3D ultrasound, in the 20th week of pregnancy. No genetic change was detected. A more in-depth examination in the second year of life found a deletion in the area 15q14q15.1. ” - del 15q14q15.1

“ We were offered genetic testing at eight months old after a private consultation indicated that our child had faltering growth and developmental delay. ” - del 15q14

Pregnancy

Information is limited, but most pregnancies and births appear to have been uncomplicated. There is one report of prenatal diagnosis of a *de novo* 4.9 Mb 15q14 deletion that was detected following amniocentesis at 23 weeks when a rare heart condition called tetralogy of Fallot (TOF) was noted during a routine scan (Chen 2016). A *Unique* baby was also diagnosed prenatally with TOF, while too much amniotic fluid (polyhydramnios) was also observed.

New-born babies

Signs of difficulty at birth were more common but not universal. Several parents described their new-born baby as very placid, sleepy or quiet, a feature that may alert doctors to an underlying condition. A few parents told us that their baby was jaundiced and many babies experienced difficulties with feeding. One baby was diagnosed at birth with cerebral palsy.

Where recorded, birth weight, length and head circumference were generally reported to be within the normal range, although some babies were born small (Chen 2008; Roberti 2011; Unique).

Growth & Feeding

Some babies and children with a 15q14 deletion have a short stature and/or an unusually small head (microcephaly). Among them were a boy with a 5.6 Mb deletion and a girl with a 2.9 Mb deletion, both affecting only 15q14, who had weight, height and head circumference measurements below the third centile. For many, growth patterns appear to be within the normal range (Chen 2008; Roberti 2011; Johansson 2014; Verheije 2019; DECIPHER; Unique).

Babies with a rare chromosome disorder can experience poor sucking and find feeding very tiring, which may be linked to low muscle tone (hypotonia). This may mean that it takes a long time to feed or babies may need to be fed more often. Anomalies of the palate may exacerbate these problems.

Although some parents told us that their baby had no early feeding difficulties, for others feeding was more challenging. Some babies experienced reflux, which could be severe, and required tube-feeding. Other parents mentioned colic and constipation. Problems generally appear to have been temporary and didn't persist into childhood (Louw 2015; Fujita 2016; Unique).

Appearance

There may be little sign in the appearance of babies and children with 15q14 deletions of the underlying disorder. Doctors may notice what are known as unusual (dysmorphic) features and you may notice similarities with other children with a comparable deletion. Among the most common features

noted among children with a 15q14 deletion were low-set or unusually-shaped ears; under-developed nostrils (hypoplastic nasal alae) or other unusual nasal features; a pointed chin; finely arched eyebrows; and a narrow forehead. A few children in medical literature had a receding lower jaw (retrognathia) (Erdogan 2007; Brunetti-Pierri 2008; Chen 2008; Roberti 2011; Johansson 2014; Chen 2016; Verheije 2019; DECIPHER; Unique).

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

Babies and children with a 15q14 deletion are likely to take more time to reach their developmental milestones, including rolling, sitting and walking. This delay was often mild to moderate and most had learned to walk somewhere between the ages of 14 months and three years. Some babies and children had reduced muscle tone (hypotonia), which can make a baby or child feel floppy to handle, or occasionally increased muscle tone (hypertonia). Cases of hypermobile joints (joint laxity) (*see* Joints & limbs) and developmental co-ordination disorder (DCD) (dyspraxia), a motor skills condition that affects co-ordination and how a child moves, were also reported. Regular physiotherapy (PT) usually proves beneficial, and the use of orthotics, such as support boots, if needed, may help increase mobility (Erdogan 2007; Brunetti-Pierri 2008; Roberti 2011; Johansson 2014; Shimojima 2017; Verheije 2019; DECIPHER; Unique).

“ He sat unaided at nine months, took first steps at 14 months and crawled later at 16 months. He didn't like tummy time at all (possibly due to torticollis [a tilted and twisted neck]). His torticollis was still evident at 18 months and his walking was still not confident; he could not get himself to standing or get back down. He couldn't break his fall either. We had lots of falls and accidents, which was awful to witness. We could not take our eyes off him for a minute. It was at this time that we self-referred to a chiropractor, who worked wonders on him. She dealt with the torticollis, as well as addressing all of his primitive reflexes, which were still intact when they should have integrated naturally at about nine -12 months. It was these that were hindering his physical progression in our eyes. After six months of twice-weekly appointments with her, he was a different boy! He could walk confidently, but unfortunately still didn't have the same physical ability as other two year olds. He could run, but it was laboured. We saw a portage worker once a week for an hour, which he loved and I found helpful and reassuring. ” - del 15q14

“ He had mild developmental delay and walked aged two. He's now learning to read and write in reception. ” - del 15q14

“ Our daughter had significant hypertonia and significant developmental delay until the age of five. Since then there have been clear improvements in small steps and today her development is proceeding as expected.

Hypertonia improved with age, and swimming, horseback riding and Kung fu helped. ” - del 15q14q15.1

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

Fine motor skills are essential for tasks such as holding a bottle, using cutlery, playing with toys, holding a pencil and fastening clothes. Information is extremely limited, but it seems that difficulties with hand use and hand-eye coordination is to be expected.

Early intervention and occupational therapy (OT) in order to improve these skills can prove beneficial for many children. Threading, jigsaws, dot-to-dot pictures, peg boards and shape-sorters can all be helpful (Unique).

As a result of these difficulties, children may also require assistance in tasks such as dressing; brushing teeth; and washing and toileting, for longer than expected (Unique).

“ Using cutlery and pencils is problematic but we are receiving OT to develop these skills. ” - del 15q14, 5 years

“ Poor grip strength. ” - del 15q14, 9 years

“ Motor skills were a problem until eight years. ” - del 15q14, 9 years

Ability to learn

Some degree of intellectual disability (ID), often mild to moderate, seems to be a common feature of 15q14 deletions. In medical literature, a 33-year-old woman with a 0.6 Mb deletion was described as having normal intellectual development; a three-year-old girl with a 1 Mb deletion had mild ID; a boy with a larger 5.4 Mb deletion had moderate ID; and a boy with a 5.6 Mb deletion had an IQ of ~50, which is consistent with moderate ID.

It has been suggested that 15q14 deletions where the *MEIS2* gene is completely deleted, or that involve other genes or extend into other bands, may be more likely to be associated with a moderate to severe ID than those with a partial deletion affecting *MEIS2* alone (or mutations in *MEIS2*). This suggests that another gene(s) close to the *MEIS2* gene may also play a role in learning and the development of motor skills (Verheije 2019).

There isn't much detailed information relating to schooling in medical literature. We do know that a six-year-old girl learned to read at the same age as her peers, but otherwise had considerable learning difficulties. Where we have information from *Unique* families, children generally attended a mainstream school for their primary school education, with dedicated support for specific areas of concern (Erdogan 2007; Chen 2008; Roberti 2011; Johansson 2014; Shimojima 2017; Verheije 2019; DECIPHER; Unique).

For some with a more severe ID, 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.

"At nearly seven years he is in mainstream school with some support, but is not statemented." - del 15q14, UK

"He is in a local mainstream school. He attended the nursery there and is very settled. There are additional adults in the class who help him when necessary. We are monitoring him this year with the school but we've been told that his needs are not great enough to apply for an EHC plan. He avoids learning new skills but is encouraged by seeing what his peers can do. He is more able at counting/mathematical skills and recall - remembering dates, specifically." - del 15q14, 5 years, UK

"Mainstream primary school, with an EHC plan, but looking at specialist secondary school. His areas of strength are maths and memory." - del 15q14, 9 years, UK

"Our daughter has dyslexia and mild intellectual disability. She began writing at five years and reading at six years. We applied for support for speech and motor skills, in addition there was a deficit in dealing with other children - large groups, lack of rituals or new situations made life more difficult. The application process for support was easy and turned out to be very important. Small groups, rituals and silence have worked well. She is in a state (public) primary school with a helper. Her ability has improved over time." - del 15q14q15.1, 10 years, EUROPE

Speech & Communication

Information relating to speech and communication suggests that some degree of language delay or difficulty with speech appears to be common, although there is considerable variation in the degree and some children appear to be unaffected.

It has been suggested that genes within 15q14 may be associated with oral-motor skills (how the muscles of the face move, which can affect speech), the ability to form the sounds of speech (articulation), and the ability to store and recall the sounds of speech in the short term memory (phonological memory). Anomalies of the palate can also affect speech (*see* Anomalies of the palate) (Stein 2006; Chen 2008; Roberti 2011; Gambin 2017; Shimojima 2017; DECIPHER).

Limited information from *Unique* parents indicated that there was improvement with time and several children used long, complex sentences. One *Unique* parent mentioned that their child had articulation difficulties making it difficult to make clearly intelligible speech sounds, which can make communication with strangers a challenge, but this also improved with time. A nine-year-old boy spoke with a nasal sound due to an anomaly of the palate and often repeated noises and phrases (echolalia). His language development was also delayed, which meant he received special education. One boy who was listed in DECIPHER and had nasal speech also had a cleft palate (Chen 2008; Roberti 2011; Johansson 2014; Gambin 2017; Shimojima 2017; DECIPHER).

Where individuals have limited speech, communication may be enhanced through augmentative/alternative communication (AAC) e.g. Makaton, signing, gesture, facial expression, Picture Exchange Communication System (PECS) and iPad communication. This 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 area(s) of need. Speech therapy has proved beneficial to *Unique* families affected by RCDs, including several with 15q14 deletions. Any concerns around hearing should also be acted on early to help reduce any impact on speech.

"No speech delay. He speaks using full sentences in an age-appropriate manner." - del 15q14, 5 years

"Started to speak at three years. He had his own language and repeated a lot and had a vocabulary of 15 or so words that he used regularly. He now speaks in long, complex sentences." - del 15q14, 9 years

"Significant speech delay. There used to be a difference in her receptive [understanding] and expressive [use of language] abilities, until the age of eight. She found it hard to make the sounds of speech and it was difficult to understand pronunciation up to six years of age, when there was a significant improvement." - del 15q14q15.1, 10 years

Personality

The testimony we have from *Unique* families speaks to children who are fun, loving individuals. It is important to remember that every child is an individual and not all personality traits will be related to the chromosome disorder.

"He is fun, chilled and likes his own company. He loves bubbles, spinning things, technology and watching number countdowns." - del 15q14, 9 years

“ He is a real treasure of a boy: sociable, likes a good laugh and very loving. ” - del 15q14

“ He's a typical boy who likes cars, Batman and dinosaurs. He loves to play with other children. Enjoys watching older children play computer games and he likes to play on his tablet. He also enjoys trampolining and playing outside, but he is a homebody and looks forward to the weekends and family time. He loves putting on shows and entertaining the family on special occasions. ” - del 15q14, 5 years

“ For a very long time she was anxious, introverted and unconsciously perceived that something was different. Today she is an incredibly positive, life-affirming child who understands part of her past and has become an integral part of a group of children through her empathic ability. ” - del 15q14q15.1, 10 years

“Challenging” behaviours & social, emotional & anxiety disorders

Some children with rare chromosome disorders, including 15q14 deletions, may on occasion exhibit shyness, anxiety, tantrums or other “challenging” behaviours. They may also recognise differences between them and their siblings or peers, which can lead to frustrations or difficulties interacting with their peers. Some behaviours may be due to difficulties in areas such as comprehension and communication. Efforts to take this into account and introduce appropriate strategies to tackle these difficulties may therefore be beneficial (*see Unique*'s guide to Behaviours) (Unique).

“ He's sweet and compliant at school but gets tired after a long day there, which makes him behave poorly at times. He's no different to any other five-year-old boy, except when he's upset he will have a major tantrum and throw things. His symptoms are mild and he also has a very sweet and caring side. His challenging behaviour is only in the presence of family. He has regular massage which really settles and calms him. A family member does this. ” - del 15q14, 5 years

“ She had difficulties in large groups, making new connections and anxiety in new situations. This made her sad and angry, but she found a way to solve this - also through support by a psychologist - and does not have these problems today. ” - del 15q14q15.1, 10 years

Some children with a 15q14 deletion have received a diagnosis for a specific social, emotional or anxiety disorder, including an autism spectrum disorder (ASD), anxiety, attention deficit hyperactivity disorder (ADHD) and sensory processing disorder (SPD), although they don't appear to be a consistent feature. Autism is a spectrum disorder and affects people in different ways and to a varying degree, but is associated with impaired social skills;

problems with communicating; and a need to carry out repetitive and restrictive behaviours, interests and activities, from which an individual derives comfort.

In medical literature, these included a three-year-old boy who was described as having an ASD with a tendency to make a distinctive and prominent sound when in a noisy room. A six-year-old girl was also described as having problems with social skills that weren't associated with intellectual disability. A boy listed in DECIPHER could become aggressive and demonstrated behaviours associated with autism. Another had anxiety and ADHD (Johansson 2014; Gambin 2017; Shimojima 2017; Verheije 2019; 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.

"Prefers his own company. Has been given an ASD diagnosis and has sensory processing disorder." - del 15q14, 9 years

Sleep

A few *Unique* parents of children with a 15q14 deletion had experienced issues around sleep. 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.

“ He has problems getting to sleep, but he has enough sleep generally because we'll start the bedtime process earlier. ” - del 15q14, 5 years

Puberty & Growing up

Some families of children with a chromosome disorder and behavioural or learning difficulties are particularly concerned about the onset of puberty. When this guide was written, we didn't have information relating to what to expect for girls and boys with 15q14 deletion, but *Unique*'s guide to "Puberty" provides helpful information if you have any concerns.

Medical concerns

General well being

While *Unique* families who took part in the 2020 survey used terms such as "very good" to describe their child's current general state of health, many parents did tell us that their child was particularly susceptible to infections during the first few months and years, including colds and other respiratory infections (Unique).

“ In his first year, he was hospitalised twice for respiratory infections but has had none at all since the age of two. As a five-year-old, he's in excellent health and rarely has any illnesses. ” - del 15q14q15.1, 5 years

“ The first months and years were marked by numerous infections (pneumonia, tonsillitis, stomach problems etc.). Today, her health is very good and she is very active and vital. ” - del 15q14q15.1, 10 years

Anomalies of the palate

Anomalies of the palate (roof of the mouth) have been observed in the majority of babies and children with a 15q14 deletion, although not everyone is affected and unfortunately we don't have specific information relating to several children. At least five *Unique* members had a bifid uvula and three a cleft palate. Anomalies can cause difficulties with feeding, hearing, teething and speech production.

Anomalies of the palate range from those that may be invisible to the casual onlooker, such as a high/arched palate, to anomalies such as bifid uvula or cleft palate (where there is a split or fork in the palate, often only the soft palate) to cleft lip and palate (where there is a split or gap in the upper lip and the roof of the mouth). A cleft occurs if, early in pregnancy, the separate parts of the developing baby's face (in this case the palatal shelves) don't join together properly.

Babies with a cleft palate may have trouble creating the suction that is needed to feed from a standard bottle or the breast. Feeding difficulties may be reduced by using special bottles or adjusting the positioning of baby on

the breast. A cleft specialist nurse should be able to provide you with more information.

Clefting can make babies more susceptible to ear infections and glue ear (where there is a build-up of sticky fluid in the ear), which can affect hearing. Where necessary, aeration tubes (grommets) may need to be fitted, while a hearing aid may help where hearing is more seriously affected. Hearing problems can also have an impact on speech development, and anomalies of the palate can make speech production difficult meaning speech is unclear. Speech and language therapy is therefore recommended where there are concerns. It is important to recognise that not all children with a cleft will experience difficulties with speech and will develop speech as expected. The degree of any difficulty is also not always related to the severity of the cleft.

In *Unique*'s experience, babies and children with a chromosome disorder generally have a higher rate of dental problems than typically-developing children (*see* Teeth), which may be exacerbated by anomalies of the palate. Depending on the type of cleft, children may require orthodontic treatment for their teeth and a high standard of dental care is particularly important. Children and adults may also benefit from specialist hospital dental services.

Surgery may be recommended to correct a cleft palate and is usually carried out within the first year of life. In at least two cases relating to a 15q14 deletion in medical literature, the cleft palate was successfully repaired before one year of age. More information can be found at www.clapa.com (the Cleft Lip and Palate Association) (Erdogan 2007; Brunetti-Pierri 2008; Chen 2008; Roberti 2011; Johansson 2014; Chen 2016; Shimojima 2017; Verheije 2019; DECIPHER; Unique).

Heart

A heart condition has been reported for just under half of those with a 15q14 deletion in medical literature, including deletions extending to neighbouring bands. Although heart conditions were associated with some deletions (and mutations) in the *MEIS2* gene, they appear to be more common where the deletion also includes the *ACTC1* gene, (*see* The *ACTC1* gene, pg 20) (Verheije 2019; Frank 2019; DECIPHER; Unique).

A ventricular septal defect (VSD), where there is a hole between the two lower chambers of the heart, appears to be the most common anomaly in babies and children with 15q14 deletions, with at least six confirmed cases in medical literature and two affected *Unique* members (Chen 2008; Crowley 2010; Johansson 2014; Verheije 2019). VSD is usually diagnosed in the first few weeks of life during routine checks. Treatment of VSDs depends primarily on the size of the hole. If the hole is small it may cause no symptoms and will just require monitoring. It may also close of its own accord during childhood. Larger VSDs may cause noticeable symptoms,

The *ACTC1* gene

Location: 15q14

35,080,297-35,087,927 (GRCh37/hg19)) (from NCBI)
34,790,230 - 34,795,549 (GrCh38/Hg38) (from NCBI)

The *ACTC1* (Actin, Alpha, Cardiac Muscle 1) gene codes for a protein called cardiac muscle alpha actin, which is one of the major proteins found in cardiac (heart) muscle. It has been suggested that having a missing copy of *ACTC1* may contribute to the heart defects associated with 15q14 deletions, since having too little of the cardiac muscle alpha actin protein coded for by the *ACTC1* gene is linked to atrial septal defects (ASDs) and ventricular septal defect (VSDs).

Mutations in *ACTC1* are associated with thickening or dilatation of the heart muscle (cardiomyopathy). It is unclear whether people with 15q14 deletions, including *ACTC1*, are predisposed to cardiomyopathy. Therefore, lifelong follow-up by a heart specialist is recommended, even in the absence of a congenital structural heart defect (Erdogan 2007; Chen 2008; Chen 2016; Frank 2019; Verheije 2019; Xefteris 2019).

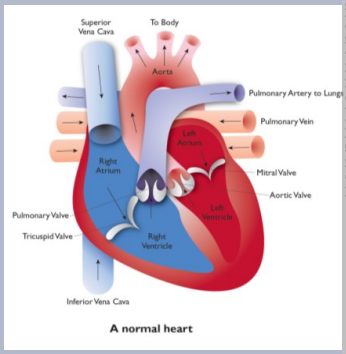
such as faster breathing, and babies may get tired when feeding. In these cases, doctors usually recommend surgery to close the hole in the first three months of life. Further cases of heart anomalies associated with 15q14 deletions included atrial septal defect (ASD), Tetralogy of Fallot (TOF), Ebstein's anomaly of the tricuspid valve, Mitral valve prolapse (MVP) and persistent foramen ovale (PFO) (*see* Types of heart condition, pg 21).

It has been suggested that a cardiologic follow-up should be recommended where an individual has a 15q14 deletion including the *ACTC1* gene, even when no heart defect is present at birth (Erdogan 2007; Brunetti-Pierri 2008; Chen 2016; Verheije 2019; DECIPHER; Unique).

"He had a check at seven weeks and the GP noted a heart murmur and sent off a referral to a consultant at the nearest hospital. It was then that he started to have laboured breathing and started to sweat when feeding. He had an appointment with a paediatric cardiologist at eight weeks, where they diagnosed two large atrial septal heart defects and a large ventricular septal heart defect. He was going into heart failure and was operated on within the week (open-heart). Post-surgery he was moved onto the high calorie formula Infatrini, to aid his weight gain and recovery. He recovered well and, by seven months, was off all medication and given a clean bill of health." - del 15q14

"She was born with a Tetralogy of Fallot." - del 15q14q15.1

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" and no treatment is required, but sometimes corrective surgery may be needed.

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. 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.

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.

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.

Tetralogy of Fallot: Tetralogy of Fallot is 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.

Ebstein's anomaly of the tricuspid valve: Ebstein's anomaly is a rare defect of the tricuspid valve. In those affected, the tricuspid valve sits lower than normal in the right ventricle, causing some blood to "leak" because the valve doesn't close properly. As a result, the right side of the heart could work less efficiently and surgical repair of the tricuspid valve may be required.

Head & Brain

An unusually small head (microcephaly) was reported in almost half of people with a 15q14 deletion in medical literature (Verheije 2019) but was not mentioned by *Unique* families. Two *Unique* children were described as having an unusually large head (macrocephaly) and two had "wry neck" (torticollis).

"We noticed that from about six months, he had a head tilt to the left hand side and backwards. Torticollis was diagnosed at 12 months. Treated by a chiropractor." - del 15q14

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. Very rarely, under MRI, anomalies of the brain were reported in association with 15q14 deletions. These included individual cases of ventriculomegaly (the fluid-filled spaces of the brain are larger than normal), broad sulci (the grooves on the surface of the brain) and cerebral palsy (Verheije 2019; Unique).

Hearing

Hearing appears to be generally unaffected, but some children had recurrent ear infections or glue ear. Glue ear is caused when a sticky fluid (glue) builds up inside the ear, which can interfere with hearing. Glue ear is typically treated by inserting aeration tubes (grommets) into the eardrum and on occasion this surgical operation may need to be repeated. As children are at risk of speech delay, parental concerns should be acted on early (*see* Anomalies of the palate) (Johansson 2014; Verheije 2019; Unique).

Hands & Feet

Children with a 15q14 deletion may have minor anomalies of the hands and feet, although there are no consistent features and not all children appear to be affected. Among the features reported were flat feet (pes planus), short fingers (brachydactyly), fingers that are unusually long and slender (arachnodacyly), broad thumbs, a single palmar crease and fingers or toes that curved inward (clinodactyly) (Verheije 2019; DECIPHER; Unique).

Limbs & Joints

Joint hypermobility (laxity) appears to be relatively common 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 had unusually short limbs. A *Unique* boy had a problem with his hip and needed to undergo a surgical operation (osteotomy) when he

was eight years old (Verheije 2019; DECIPHER; Unique).

Minor anomalies of the genitals (boys)

The experiences of several *Unique* families and a few cases documented in medical literature suggest that some boys may be born with undescended testis/testes (cryptorchidism). The testes begin their descent from the abdomen when a baby is still in the womb and have usually arrived in the scrotum by birth. In a significant number of boys without any chromosome abnormality, that journey is not complete by birth but is completed within the next few months of life. When descent does not occur, the testes can be brought down in a surgical operation (orchidopexy) and anchored in the scrotum, as was the case for at least two boys within the *Unique* series who underwent successful operations at 12 months.

"It was also noted in hospital that he had a right undescended testicle. He had his testicle operated on at 12 months of age (orchidopexy). This all went well." - del 15q14

Café-au-lait spots (macules) (CALs)

Café-au-lait spots (CALs) are flat, pigmented spots that have a characteristic light brown colour, similar to milky coffee. They can vary in size, ranging from the size of a freckle to several centimetres in diameter.

CALs have been reported in a number of individuals with 15q14 deletions that include the *SPRED1* gene, both in medical literature and among *Unique* members. CALs are also one of the features of a rare genetic disorder called Legius syndrome. Legius syndrome is known to be caused by changes (mutations) in the *SPRED1* gene, which is located in 15q14 (Johansson 2014; Verheije 2019; Unique).

Teeth

Dental problems are very common in children with chromosome disorders and a high standard of dental care is important to minimise damage by decay and erosion. Among *Unique* families data is limited, but several mentioned late teething and tooth grinding (bruxism). A 10-year-old girl with a deletion involving 15q14 and 15q15.1 had weak enamel (enamel hypoplasia) and over-crowding that required orthodontic treatment with braces. There are very few reports of concerns in medical literature, although several children had large front teeth (central incisors) (Verheije 2019; Unique).

Other medical concerns

Generalized epilepsy: Chen 2008 (15q14 deletion)

Prolapse of the epiglottis into the larynx and laryngomalacia. Underwent supraglottoplasty surgery at one year of age: Chen 2008 (15q14 deletion)

A squint (strabismus): One case *Unique* (15q14 deletion)

Long-sightedness (hyperopia): One case *Unique* (15q14 deletion)

Short-sightedness (myopia): One case Verheije 2019 (15q14 deletion)

Mild kyphoscoliosis (outward and sideways curvature of the spine): One case Roberti 2011 (15q14 deletion)

Inguinal hernia: One case DECIPHER (15q14 deletion)

Families say...

“Each child is different. You have to look at their needs as an individual. We have found time is the best indicator of what our son's needs are and we have come to understand him much better over the years.”

“We consider it a gift to have a child who has learned in many small steps over a long period of time, things that others take for granted. We appreciate the small things and it is not only about being the best.

Uncertainty was certainly the most stressful situation right from the start. You may lose friends who were not. You reorganise your life. But it also gives you an unbelievable amount of strength if you get involved and meet the child with love. After 10 years, we are now immensely proud that our daughter is a strong, life-affirming and intelligent child.”

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)

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

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

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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.

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

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed.

This booklet was first compiled by Unique (CA) in 2020 and reviewed by Dr Jeroen Breckpot (MD PhD), Centre for Human Genetics, Catholic University Leuven, Leuven, Belgium and Prof Gunnar Douzgos Houge (MD PhD), Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway.

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