Unique

Understanding Chromosome & Gene Disorders

5q14 duplications

rarechromo.org

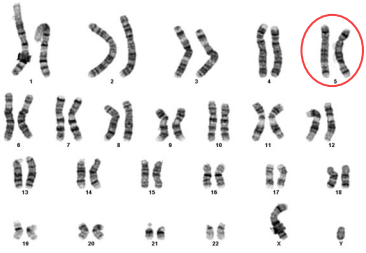
5q14 duplications

A chromosome 5q14 duplication is a rare genetic condition in which there is an extra copy of part of the genetic material that makes up one of the body's 46 chromosomes - chromosome 5. A duplication is also called a partial trisomy. As with other chromosome disorders, having an extra piece of genetic material may increase the risk of 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 5q14 duplication is variable and depends on a number of factors, including what and how much genetic material is duplicated.

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.



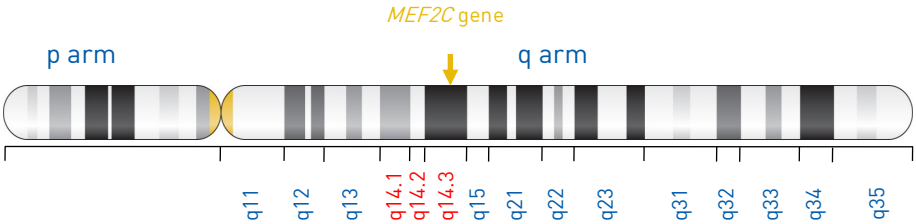
Chromosome pairs 1-22, X and Y (male). Chromosome 5 pair circled in red

A normal cell in the body has 46 chromosomes that are numbered 1 to 22, approximately from largest to smallest, apart from the sex chromosomes (two Xs for a girl and an X and a Y for a boy).

Looking at chromosome 5

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 in the diagram on the next page.

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 q11 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 q33 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.



People with a 5q14 duplication have one normal chromosome 5, but the other chromosome 5 has an extra piece of chromosomal material from all or part of band q14 on the long arm, which includes q14.1, q14.2 and q14.3.

The 5q14.3 band contains a gene called *MEF2C* (*see* blue box on page 4). Loss (deletion) or changes (mutations) to *MEF2C* that mean that one copy of the *MEF2C* gene does not function normally have been shown to be responsible for the major features of 5q14.3 deletion syndrome (also known as *MEF2C* haploinsufficiency syndrome) (Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Nowakowska 2010; Zweier &Rauch 2012; Vrečar 2017; Decipher; Unique) (*see* 5q14.3 deletion syndrome/*MEF2C* haploinsufficiency syndrome, page 9).

The consequences of over-expression of *MEF2C*, usually due to a 5q14.3 duplication leading to an extra copy of *MEF2C*, are less well understood, but what is known will be discussed in this guide. Duplications involving 5q14.1, 5q14.2 and 5q14.3 that don't include *MEF2C* will also be discussed where possible, although it is important to bear in mind that this information is extremely limited and provisional. Also included in this guide is valuable information provided by several *Unique* members with larger 5q duplications including part of 5q14. It is important to recognise that duplication of genes in other bands on 5q may influence any features that are discussed.

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. Five *Unique* members completed a detailed survey in 2018/19. In addition to this, information has also been drawn from the database records of other members where possible.

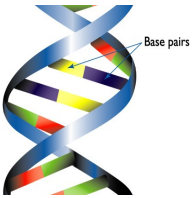
Chromosomal changes

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

Genetic tests

With any duplication the amount of duplicated DNA can vary. Duplications that are so small that they are not visible under the microscope using standard techniques, as is the case for some duplications involving 5q14, are called microduplications [microduplications are typically one to three megabases (Mb) long]. Many people who have a microduplication 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 duplication. This technique uses fluorescently labelled pieces of DNA that match the DNA in specific places on a chromosome so this test will only be offered if there is a suspected abnormality in a specific region of a chromosome.



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

The MEF2C gene

Location: 5q14.3 [88,014,058 - 88,199,922 (GRCh37/hg19)]

During development of the human body, the *MEF2C* (Myocyte Enhancer Factor 2C) gene interacts with other genes in a multigene network, playing a crucial role in brain development, as well as the development of the heart, blood vessels, immune system, muscles and face.

Recently it has been shown that MEF2C interacts with MECP2 and CDKL5, the main genes associated with Rett syndrome (Zweier 2010). Mutations in *MEF2C* from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe intellectual disability and diminish *MECP2* and *CDKL5* expression.

The presence of an extra copy of *MEF2C*, is one of the mechanisms that lead to overexpression of the related protein. This may affect this carefully controlled network of genes, for instance by causing the upregulation and overexpression of other genes in the network. This is thought to lie behind many of the features associated with 5q14 duplications (Cesaretti 2016; Yuay 2019).

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 duplications 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 duplicated, but it cannot show if the new piece of DNA has moved to a different place on the same chromosome or to a different chromosome.

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 microduplications/microdeletions that may be missed by less sensitive microarray analysis.

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 5q14 duplication could exist alongside cells with a normal chromosome number and arrangement. Mosaicism is rare, but where it has been reported in the medical literature for other rare chromosome disorders the outcome of the condition was in some cases milder, although it appears that no cases of mosaicism involving 5q14 duplications have been reported to-date.

Chromosome test results

Your geneticist or genetic counsellor can tell you more about the genes and chromosome material that have been duplicated and you will be given the results of your test, which will tell you how much of chromosome 5 has been duplicated.

Depending on the test that was carried out, someone with a duplication including 5q14 might have results that looks like one of these examples:

46,XY,dup(5)(q14.3)dn - 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. dup(5) means there is a duplication of chromosome 5. (q14.3) shows the part of the chromosome that is duplicated; in this case, there is a gain of a chromosome segment in band 14.3. The duplication occurred dn or *de novo* (as a 'new event'): the parents' chromosomes have been checked and no duplication or other chromosome change has been found so the duplication has not been inherited from either the father or the mother.

Genome Assemblies

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

arr[hg19] 5q14.3 (85129432_90182723)x3 This result shows that the analysis used microarray technology (arr). The analysis revealed a DNA anomaly involving 5q14.3. 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 85129432 and 90182723 (by taking the first number from the second, you can work out that this is 5,053,291 base pairs, or 5.05 Mb). There is an extra copy (x3; the normal copy number is two) so it is a duplication. hg19 tells you which version of the human genome was used for comparison (*see* Genome Assemblies (blue box)).

arr[hg19] 5q14.3q15(84311087_95328133)x3 This result shows that the analysis used microarray technology (arr). The analysis revealed a DNA anomaly involving 5q14.3 to 5q15 (the anomaly extends to the more distal 5q15 band). 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 84311087 and 95328133 (by taking the first number from the second, you can work out that this is 11,071,046 base pairs, or 11.02 Mb). There is an extra copy (x3; the normal copy number is two) so it is a duplication. The hg19 (GRCh37) assembly was used for comparison.

You may wish to compare your child's results with others - both in the medical literature and within *Unique* - who have the same or a similar duplication or microduplication, to help understand your child's development. While this may help identify common consequences, it is important to remember that the same duplication can have different effects

on different people and the precise effects of gaining material from a chromosome varies depending on numerous factors that we are only beginning to understand.

A child'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 duplicated piece of DNA. After all, each of us is unique.

How common are 5q14 duplications?

It is difficult to estimate the prevalence of 5q14 duplications since many people will not have been diagnosed, and many of those who are diagnosed are not reported. However, at least four cases with a 5q14 microduplication including the *MEF2C* gene have been reported in some detail in the medical literature (Le Muer 2010; Novara 2013; Cesaretti 2016).

At the time of writing, there were also 35 cases with a duplication involving 5q14 duplication and no other recorded genomic variants in the database DECIPHER (DatabasE of Genomic VarIation and Phenotype in Humans using Ensembl Resources; https://decipher.sanger.ac.uk (*see* page 31)). Of these 35 individuals, 16 had a microduplication involving 5q14.1 alone (not including *MEF2C*); one involved 5q14.1 and q14.2 (not including *MEF2C*); 12 involved 5q14.3 alone (five including *MEF2C*); four involved 5q14.3 and q15 (two including *MEF2C*); one spanned 5q13.3 and q14.3 (including *MEF2C*); and one spanned 5q14.1 and q14.3 (including *MEF2C*).

Worldwide, *Unique* had 11 members with a duplication including 5q14. One duplication involved part of 5q14.1 alone (not including *MEF2C*); one spanned 5q11.1 into 5q14.1 (not including *MEF2C*); two involved 5q14.3 alone (both including *MEF2C*); one spanned 5q13.3 to 14.3 (including *MEF2C*); two spanned 5q14.3 to q15 (both including *MEF2C*); one spanned 5q14.3 to q23.1 (not including *MEF2C*); one spanned 5q14.3 to q15 and 5q21.1 to q22.2 (including *MEF2C*); and one spanned 5q14.3q to q31.1 (not including *MEF2C*). One member had a duplication of the whole of the 5q arm (including *MEF2C*).

Note: Unique is also planning further guides to 5q duplications that may be useful to members with larger duplications and duplications involving other regions.

Why did this happen?

To answer this question, the parents' and affected child's chromosomes need to be tested. What is certain is that, as a father or mother, there is nothing you did to cause the duplication 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.

5q14 duplications are known to be either inherited from a parent or to occur *de novo* (dn), which means the duplication has occurred as a new event in the child. Four cases of 5q14.3 duplication in the medical literature were shown to have occurred *de novo*. For many of the cases listed in DECIPHER the origin of the duplication was unknown, but while there are a few confirmed cases of duplications that have occurred *de novo,* several duplications were documented as being inherited from a parent (Le Muer 2010; Novara 2013; Cesaretti 2016; DECIPHER).

Among *Unique* members with a duplication affecting 5q14 alone, in almost all cases the origin of the duplication was not specified or was unknown, while two were confirmed as *de novo*.

Regardless of the origin of the duplication, as stated above, it is important to know that as a parent there is nothing you could have done to prevent the duplication from happening. No environmental, dietary or lifestyle factors are known to cause 5q14 duplications. There is nothing that either parent did before, during or after pregnancy that caused the duplication.

Can it happen again?

Where both parents are determined to have "normal" chromosomes, it is very unlikely that another child will be born with a 5q14 duplication 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 5q14 duplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 5q14 duplication rises to 50% (1 in 2) in each pregnancy. However, the effect of the duplication on the child's development, health and behaviour cannot be reliably predicted. Your genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a 5q14 duplication goes on to have children of their own, the chances of passing on the duplication to their child are 50% 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 5q14 duplication who are healthy, have no major medical problems or birth defects and have developed normally?

Yes. The DECIPHER database lists several cases of microduplications inherited from an unaffected parent, including four individuals with tiny microduplications (all less than 0.7Mb) involving 5q14.1 alone, two

individuals with microduplications involving 5q14.3 alone and an individual with a 5q14.3q15 microduplication. All were listed in DECIPHER as they had had a child who had inherited the duplication.

For many of the entries in DECIPHER where a CNV involving a duplication of 5q14 is reported, the significance and/or contribution of the 5q14 duplication to any observed feature is also listed as unknown or uncertain.

5q14.3 deletion syndrome/MEF2C haploinsufficiency syndrome

Deletions and mutations involving the *MEF2C* gene have been identified as the cause of the major features of 5q14.3 deletion syndrome/MEF2C haploinsufficiency syndrome (also known as "mental retardation, autosomal dominant 20" (MRD20) (*see* page 3)). It is believed that when one copy of the *MEF2C* gene is missing or changed, the remaining copy of the gene on the normal chromosome 5 can not produce enough of the gene product to allow the cell to function as normal (haploinsufficiency).

Not all people with 5q14.3 deletion syndrome/MEF2C haploinsufficiency syndrome have the same features but the most frequently reported features are: variable degrees of developmental delay; intellectual disability, which is often severe; severely impaired or absent speech; hypotonia (low muscle tone); seizures; stereotypic movements; variable anomalies of the brain; and characteristic (though subtle) facial features. Those with a chromosome 5q14.3 deletion that also affects other genes can have an increased likelihood of medical problems compared to those with mutations or deletions limited to the *MEF2C* gene.

As the number of reported cases of 5q14.3 *duplications* increases, researchers are beginning to conclude that duplications involving this band of chromosome 5 can also lead to certain features, with some overlap with those associated with deletions. As is the case for a number of other duplications affecting other bands of other chromosomes e.g. 7q11.23 microduplications and 16p13.11 microduplications, the features associated with *duplications* involving 5q14.3 appear to be milder than those of *deletions* involving 5q14.3.

As with 5q14.3 deletion syndrome, overexpression of *MEF2C* due to 5q14.3 duplications (or other causes that lead to over expression of *MEF2C* (*see* below)) is thought to be responsible for many of the features associated with 5q14.3 duplications (Cardoso 2009; Engels 2009; Berland 2010; Le Meur 2010; Nowakowska 2010; Zweier &Rauch 2012; Novara 2013; Cesaretti 2016).

Unique has guides to "5q14.3 deletions" & "MEF2C haploinsufficiency syndrome (MRD20/chromosome 5q14.3 deletion syndrome)".

Can someone have features associated with 5q14.3 duplications without the *MEF2C* gene being duplicated?

Yes. There are a number of ways in which this can happen, including the examples below.

While duplicated material usually includes all or part of one or more genes that are important for normal development, such as the *MEF2C* gene, sometimes the duplication does not include part of a gene but consists of/disrupts material close to a gene. This can also affect the expression of that gene even if the gene itself isn't duplicated.

Another possible mechanism has been described in the medical literature, where there is a report of a girl with a balanced translocation between chromosomes 3 and 5. Balanced translocations occur when a section from one chromosome of a particular pair changes places with a section from a chromosome of another pair but there is no gain (duplication) or loss (deletion) of material. Although the breakpoints on chromosomes 3 and 5 revealed that no genes were interrupted, one of the breakpoints was found to be very close to the *MEF2C* gene resulting in increased *MEF2C* expression and features similar to those associated with 5q14.3 duplications involving *MEF2C* (Yuay 2019).

5q14 duplications involving 5q14.1 & 5q14.2

Less is known about the genes linked to the features associated with 5q14 duplications involving 5q14.1 and/or 5q14.2. There is an overlap in features with 5q14.3 duplications, although an association with overgrowth/obesity seems to be a feature that is distinct to 5q14.1 duplications, while autistic traits/autism also appears to be more common among children with a 5q14.1 duplication. At present, there is no data relating to 5q14.2 duplications alone to draw upon.

Common Features

Just as "typically"-developing children can experience a number of unforeseen physical and behavioural difficulties, each person with a 5q14 duplication is unique and can have different developmental and medical concerns. However, the most likely features associated with 5q14 duplications, and/or those that are the most likely to make a difference to a child's health or development, are:

- Some degree of developmental delay (often mild)
- Some degree of intellectual/learning disability
- Delayed/absent speech
- A small head (microcephaly) (5q14.3 duplications including *MEF2C*)
- Autism or autistic traits (5q14.1 duplications)

Other features

Other features have been noted in the medical literature and among *Unique* members with a 5q14 duplication. Some are known to be generally more common in children with chromosome disorders; others may in fact be unconnected with the chromosome disorder. All the same, they have occurred in other people with a 5q14 duplication and include:

- Feeding difficulties
- Seizures
- "Challenging behaviours"
- Problems with vision/structural eye anomalies
- Low muscle tone (hypotonia)
- Frequent ear infections/glue ear, which usually resolve during childhood
- Short stature (5q14.3 dups including *MEF2C*)
- Overgrowth/obesity (5q14.1 duplications)
- Minor differences of the hands and feet
- A brain anomaly
- Minor dental concerns

(Le Muer 2010; Novara 2013; Cesaretti 2016; Yuay 2019; DECIPHER; Unique)

Diagnosis

The majority of *Unique* members were offered genetic testing between 20 months and two years, 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).

"Genetic testing was offered at around two years. Our doctor picked up delays at the nine-month check-up, as our daughter had been receiving various therapies and had developmental delay, although she was within the expected limits. The doctor suggested testing, and we accepted after reflection. It took more than a year for the results to come in but it was helpful to have a diagnosis." - dup 5q14.3q15

Pregnancy

While medical literature relating to 5q14.3 duplications (all involving *MEF2C*) included several cases of uneventful pregnancies, a scan revealed slow growth in the womb (intrauterine growth retardation (IUGR)) in one report, while separately both twins in a pair were found to have a number of congenital anomalies, including anomalies of the brain (Novara 2013; Cesaretti 2016; Yuay 2019).

Among *Unique* members, pregnancy usually proceeded to term without major concerns for the fetus. One baby was induced due to a reduced level of amniotic fluid and one mother experienced hyperthyroidism. One fetus was monitored closely because of a risk of autoimmune congenital heart block (CHB) due to the presence of SSA/RO antibody in the mother, with a scan revealing that the fetus's heart was normal.

New-born babies

Information is limited, but at least five *Unique* babies showed some signs of difficulty at birth, regardless of duplication size. Three babies were jaundiced and two required treatment with phototherapy. One parent described their new-born baby as "unusually inactive and placid", a feature that may alert doctors to an underlying condition. Another baby made unusual "grunting" noises when he was born. Many *Unique* babies, and two in the medical literature, experienced difficulties with feeding (*see* Feeding) (Novara 2013).

The average birth weight of three *Unique* babies and two babies in the medical literature with a 5q14.3 duplication involving *MEF2C* was 6lb 9oz (2.97kg) (range 5lb 5oz - 7lb 14oz) (Novara 2013; Unique).

Growth & Feeding

Although some parents told us that their baby had no early feeding difficulties, for others, regardless of the size of the duplication, 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 (Novara 2013; Unique).

The most common concerns were around poor sucking and finding feeding very tiring, which may be linked to low muscle tone (hypotonia). This may mean that it takes a long time to feed or baby may need to be fed more often.

A few babies suffered from reflux, 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. A surgical operation called a fundoplication can improve the action of the valve in the most serious cases, although this does not seem to have been necessary in the cases we know about (Novara 2013; Unique).

Constipation is common among children with chromosome disorders but appeared to be uncommon in babies and children with 5q14 duplications. Where there are concerns, it is important that parents discuss the possible causes with their health visitor or doctor, who may recommend adapting a child's diet or giving stool softeners such as Movicol or laxatives such as Lactulose and Senna.

Longer term, some children with 5q14.3 duplications including *MEF2C* seem to be on the small side; others are nearer average weight and height. No parents reported any cause for concern regarding eating habits or growth (Le Meur 2010; Novara 2013; Unique).

There is limited evidence to suggest that 5q14.1 duplications (not including *MEF2C*) are associated with overgrowth or being overweight (Unique; DECIPHER).

The few children we know about with larger 5q duplications including part of 5q14 appeared to experience more problems with feeding (see comments).

“ He wasn't thriving with breast milk so started on formula after a couple of weeks. He vomited a lot so we tried many different formulas, finally settling on a hypoallergenic one. At four months he had a barium swallow test, which confirmed reflux. Started on daily medication to help with symptoms of acid reflux, which he has outgrown.

At 10 years, he is on the 45-50th centile for height and the 75th centile for weight. He has good muscle definition in his legs from all the physical therapy. He has had constipation off and on over the years. In addition to fresh fruits and vegetables, we use probiotics and Miralax to treat this. He eats a wide variety of foods, including fruits and vegetables, though he does not like lettuce or onions, which we believe is due to the texture. He loves steak, chicken and fish. ” - dup 5q14.3 (including *MEF2C*), 10 years

“ She is small but has always followed the bottom of the growth curves for weight and height. She's not really stocky but has longish legs and is very long between the hips and waist. Our child is a good eater, she eats what she needs and is not tempted by food from looking at it. She eats good portions and enjoys all foods. ” - 5q14.3q15 (including *MEF2C*), 13 years

“ We were told he had moderate reflux but his symptoms were severe. He didn't like to eat and it was a challenge to get even a couple of ounces of formula down. He was prescribed medication and special formula to help the symptoms. This seemed to help and the reflux resolved by two years. Now he just carries a few extra pounds on his tummy. ” - dup 5q11.1q14.1 (not including *MEF2C*), 7 years

“ Growth has not been identified as an issue, but he is small (2nd centile). We did struggle with weaning. He started OK with small tastes, but when he was eating good amounts of mushed food he would violently throw it up (through his nose). This went on from about 8 to 11 months and stopped of its own accord. ” - dup 5q14.3q23.1 (not including *MEF2C*), 18 months

“ She was slow to put on weight due to exhaustion from feeding (could only feed for five minutes at a time). Took six weeks to regain birth weight and was then tracking at 9th centile for weight for the first year, but had a growth spurt at three-and-a-half years and is now on the 50th centile for height. She

has dysphagia (swallowing problems) so we use thickener in her milk. She is limited to milk and water for drinks, prefers soft foods and struggles with protein. She chokes on fruit and vegetable peel and has assisted seating to help her. " - dup 5q14.3q31.1 (not including *MEF2C*), 4 years

Appearance

Overall, it appears that there is no particular "look" associated with babies and children with a 5q14 duplication, but you, or particularly geneticists or doctors trained to note unusual (dysmorphic) features, may notice some slight differences. These are likely to be subtle if present. Features such as high/arched brows; low-set or unusually-shaped ears; a nose with a broad nasal bridge and tip; widely-spaced eyes; a thin upper lip; and a pointy chin, have all been noted.

Very occasionally, low facial muscle tone led to dribbling (drooling), as was the case for one boy with a 5q14.3 duplication involving *MEF2C*. If children do not outgrow dribbling, your doctor may recommend treatments such as hyoscine patches or a medicine called glycopyrrolate can be given by mouth (Le Meur 2010; Novara 2013; Yuay 2019; Unique).

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

Information from the medical literature and *Unique* members suggests that many babies and children were late to achieve their gross motor skill 'milestones', although most of what we know relates to duplications including *MEF2C* and the delay was often mild. It generally took longer than is typical for babies and children to roll over, sit, crawl and walk, although many children walked independently between 18 months and two years.

Low muscle tone (hypotonia) was common and is one of the main causes of a delay in mobility in babies and children. Hypotonia can make a baby or child feel floppy to handle. One *Unique* child with a 5q14.3 duplication including *MEF2C* had ataxia (the term used for a group of disorders that affect a person's co-ordination, balance and speech and therefore their ability to carry out gross motor skills). Apraxia was also suspected (a neurological disorder characterised by difficulties in performing familiar movements on command, even though the command is understood and the person would like to perform the movement).

Muscle tone often improves with age, with regular physiotherapy (PT) and exercise proving particularly beneficial. The use of orthotics such as support boots may also help increase mobility.

In common with their peers, many children enjoyed being active and relished a range of physical activities, including scooting, swimming and running (Le Muer 2010; Novara 2013; Yuay 2019; DECIPHER; Unique).

❝ Our son has achieved all his milestones, but most were late. He crawled at 14 months and walked at 22 months. He has hypotonia (particularly in his trunk), decreased core strength, ataxia/apraxia and what was described as a movement disorder.

He was evaluated at 9 months through a state early intervention program and began receiving weekly services for occupational, physical, and speech therapy, weekly. Developmental therapy was monthly. This continued until age three when he started in the public (state) school with an IEP (individualized education plan) (*see* "Ability to Learn" section) and he started to receive these therapies in school. We supplemented these school-based sessions privately with occupational, physical, speech, and hippotherapy (equestrian (horse)-based therapy). In PT he learned to jump, stand still, and stop on command, as well as other skills. We believe our son has benefited tremendously from these therapies and has mastered so many skills like putting his arms down when he falls to protect himself, jump, hopping on one leg, hitting a ball, riding a bike with training wheels, writing, using a keyboard, using a zipper, reading. ALL were enhanced by therapy. We highly recommend it! He enjoys bowling and riding his scooter. ❞ - dup 5q14.3 (including *MEF2C*), 10 years

❝ She has a moderate to severe global developmental delay. She walked at 20 months and by three-and-a-half her stance and walking were good, although she would lean forwards a lot and fall over her own feet. Our daughter has had PT from 9 months to help with walking, and on and off since. She likes walking and, now she can use it, her scooter. ❞ - dup 5q14.3q15 (including *MEF2C*), 13 years

❝ He has a borderline developmental delay: rolled late at 10 months, crawled late at 15 months, but walked on time at 17 months. At two years he is walking with confidence. ❞ - dup 5q14.3q23.1 (not including *MEF2C*)

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 difficulties with hand use and hand-eye coordination appear to be common among *Unique* children.

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, washing and toileting, for longer than expected (Unique).

“ Fine motor skills are delayed, including difficulties with writing, buttons, zippers, tying shoes, holding cutlery. He was potty trained for daytime starting at about three to four years of age. He does have occasional urine accidents during the day, if he's in a new place and doesn't feel comfortable asking to go to the bathroom or if he's playing and doesn't want to get up. This happens infrequently. He is not potty trained at night and still wears a pull up. ” - dup 5q14.3 (including *MEF2C*), 10 years

“ Our child has particular problems with anything to do with interpreting the amount of pressure to use or not use, and getting this message to her brain and back again so she can adjust. This makes lots of things difficult for her and they have to be worked on through occupational therapy, but improvements have been made in many areas.

She was still wearing nappies when she started school, but actual potty training once she undertook it was established in a short time and she was toilet trained by the age of five. ” - dup 5q14.3q15 (including *MEF2C*), 13 years

“ Great pincer grip and on time development. ” - dup 5q14.3q23.1 (not including *MEF2C*), 18 months

“ He is poorly coordinated with fine motor tasks and some gross motor tasks, but is getting much better. ” - dup 5q11.1q14.1 (not including *MEF2C*), 7 years

Ability to learn

Information is limited, but it appears that children with a 5q14 duplication are very likely to need early and ongoing support with their learning. Some children we know about have a mild to moderate learning disability (LD); others are more severely affected.

Two *Unique* children with a duplication including *MEF2C*, aged 10 and 13 years, had a moderate to severe LD. Two others with duplications not including *MEF2C* had a severe LD (dup 5q11.1q14.1, seven years) and a moderate LD (dup 5q14q31.1, four years).

In the medical literature, three children with a 5q14.3 duplication including *MEF2C* had a mild cognitive impairment. A 9-year-old with a balanced translocation leading to overexpression of *MEF2C* was assessed as having a developmental age of three years and was educated in a special school (Le Meur 2010; Novara 2013; Yuay 2019). DECIPHER also lists cases of individuals with intellectual disability associated with 5q14 duplications, whether or not *MEF2C* is involved, even for those with tiny duplications involving 5q14.3 or 5q14.1.

Children who attend a mainstream school are likely to benefit from 1:1 help or dedicated support workers, for specific areas of concern. For some with a

more severe LD, a school specifically for children with special educational needs may be better equipped to meet their needs. One *Unique* child was home-schooled. 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.

"When he was younger we were focused on his gross and fine motor delays but we started to notice difficulties in kindergarten, primarily with delays in reading and maths. These have continued, though with reading it's more about comprehension and understanding inferences. We are also seeing difficulty in science and social studies. He still draws stick figures and struggles to colour inside the lines, though this has improved. He started writing on time, but struggled with size and spacing of letters. He still does, but is much improved. However, we've also noticed he is very good with electronics and loves music.

He has an individualized education plan (IEP). This was originally obtained at age three, when he started in public (state) school, and is updated annually. We have been very lucky and are in a great school district where we get a lot of support and services, in addition to what we do privately.

He uses a keyboard (started at 8 years) to help with longer assignments. Starting in 1st Grade (Year 2) he was placed in a homeroom with all students and attended lunch, recess (break), music, art, social studies, science, and physical education with all his peers. He stayed in a self-contained classroom for part of the day for additional assistance with reading and maths. He is now in 4th grade with the same methodology, and services have been added over the years as needed. He also gets support in occupational, physical, and speech therapy in and out of school and now receives adapted physical education services and social work minutes.

When he doesn't understand something he tends to be disruptive to avoid the new skill or having to admit that he doesn't understand. He tends to improve more quickly when he feels confident and really enjoys something. He does well with repetition and when tasks are broken down. He is very good with electronics and searches easily on a computer or iPad to find movies, books or music he is interested in.

Our recommendation is to be a strong advocate for your child. Be visible to ensure your child gets all the tools and support available." - dup 5q14.3 (including *MEF2C*), 10 years, US

“ She has a moderate to severe LD. She is 13 and her cognitive age is closer to six or seven years, if that. While learning is hard for our child, we see more potential and aptitude is possible given the right environment.

Her drawing skills are very minimal with no difference from age six/seven years. Writing is basic but getting better. Reading is slow but is coming along. Keyboard skills are being taught and are slow, but she can input search topics and close and open files.

We pushed for integration and for the first five years of school our child split her time between a local school and a specialised school. This was quite difficult but she coped well and enjoyed it. However, the schools didn't work together (especially the local school) and she is now full time in the specialised institution she has been in since the age of four. It is a very safe environment and the children are well cared for, but it is really a crèche with a little bit of teaching. She has learnt and improved, but very much at her own slow but steady pace. Confidence has come with age but she needs lots of encouragement.

She has a good memory and is good at finding patterns in things (rather than learning the fact she tries to see a pattern). She tends to give up at the first sign of difficulty. She doesn't make the connections from one skill to another; each stage has to be learnt painstakingly and the next stage gently led onto.

Our daughter has had speech therapy, physiotherapy and occupational therapy regularly throughout her life. They have adapted to her particular problems at any one time, but they have all been essential in helping her move forward. ” - dup 5q14.3q15 (including *MEF2C*), 13 years, EUROPE

“ At four years, her learning age is that of a two-year-old. She learns through being shown hand on hand multiple times. We are in the process of converting her “My Support Plan” to an EHCP. So far, the process has been very good and we have a great team working together to support her. She is in a mainstream setting and receives one to one support; the preschool have been absolutely brilliant in meeting her needs. I felt it was important for her to stay within the local community and grow in confidence with friends that she will go to school with. I do not want to single her out as different, but need for her to be safe and supported as she develops. She has not shown any signs of regression, but is progressing at a much slower rate than most children and avoids anything she finds hard. ” - dup 5q14.3q31.1 (not including *MEF2C*), 4 years, UK

Speech and Communication

The limited information we have from *Unique* members and the medical literature suggests that speech is typically one of the most commonly affected areas of development. Speech and language development was often severely delayed, regardless of duplication size, and a few children remain

non-verbal; others go on to develop a good level of speech. Parents often mentioned that their child's comprehension of language was better than their ability to communicate using language (Le Meur 2010; Novara 2013; Yuay 2019; DECIPHER; Unique).

There are many reasons for a speech delay, including the link between the ability to learn and the ability to speak. Hypotonia can result in weakness in the mouth muscles which, as well as causing insufficient sucking, can also affect the development of speech.

Where speech does develop, with time children may use long, complex sentences. Some parents mention that their child has articulation difficulties making it difficult to make clearly intelligible speech sounds, which can make communication with strangers a challenge.

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. 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 areas of need. Speech therapy has proved beneficial to many *Unique* families affected by RCDs, including 5q14 duplications. Any concerns around hearing should also be acted on early to help reduce any impact on speech.

❝ Our daughter started to speak late and communication was difficult for the first years of school. Although now she does communicate well and makes grammatically correct phrases, it is below her age level. Lack of reading and other language-based activities at school have also meant that her exposure to language was limited, thus limiting her. She finds some sounds difficult to make and moving her tongue around quickly in her mouth to make different sounds has needed a lot of work. She has always had speech therapy, initially working on making sounds but now more to do with reading and understanding.

She is binlingual; we are English-speaking but she has learnt French at school and French is her preferred language. She can make long simple sentences e.g. "What day we going to airport?", "Me can sleep in your bed? ". She seems to understand everything. Specialists say she can understand the immediate and not the abstract, which is true to a certain extent, but sometimes she picks up a relatively complex point from a sentence not addressed to her or relevant, which surprises us. ❞ - dup 5q14.3q15 (including *MEF2C*), 13 years

❝ His speech was mildly delayed. He struggled with certain sounds at an early age e.g. th, f, n, etc. and used only short sentences. Now, he is using

more complex sentences that sometimes include complex vocabulary words. His sentences are more complex when speaking than when writing. Since writing is difficult, he tends to write short sentence e.g. "Do I have bowling this Saturday?", "Do I have an appointment with the doctor today?", "I have Sunday school today. Who is going to pick me up, you or Daddy?". We believe he understands more than he can articulate. Speech therapy (both in school and privately) greatly helped. The big areas of focus with speech therapy now are expressive and receptive language skills. " - dup 5q14.3 (including *MEF2C*), 10 years

" At five years, he cannot talk, but does make a lot of noises and communicates through pointing, making sounds and a little bit of Makaton. " - dup 5q14.3q15 (including *MEF2C*)

" Has difficulty with articulation at 10 years. " - dup 5q13.3q14.3 (including *MEF2C*)

" No words at 18 months, but he did babble. At almost two years he had about 15-20 words, but they were very unclear and he wasn't joining words together. At two years, he has been officially recognised as having speech delay, but his language is coming! He has been referred to speech and language therapy because his words are unclear and nasal (no consonants) - but he has over 20 words and has put two words together today ("all gone" & "wash hands"). " - dup 5q14.3q23.1 (not including *MEF2C*), 2 years

" Started babbling at three years. Said first word (mumma) at three-and-a-half years. We attend speech therapy weekly and she is at the stage of a 16–to 24-month-old e.g. "where dada?", "I did it.". She learns through the rhythm of words and can't say the individual words. She does Makaton when she gets stuck or frustrated and all her speech is accompanied by gestures. I believe her understanding is slightly ahead. " - dup 5q14.3q31.1 (not including *MEF2C*), 4 years

" He can repeat words and say about 10 words independently, but is minimally verbal and says two to three word phrases, when prompted mostly. He can use an AAC device, but we are slow figuring out how to help him learn to use it. He understands more than he can express. " - dup 5q11.1q14.1 (not including *MEF2C*), 7 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 happy, loving, funny and caring individuals. There appears to be a tendency for some with a 5q14 duplication including *MEF2C* to be somewhat anxious and shy around strangers or in new social situations, and some children found it easier to relate to people older or younger than themselves. Some parents told us that

their child's mood and behaviour could suddenly change, leading to challenging behaviours (*see* "Challenging behaviours").

Children enjoyed a wide range of activities, from walking, running, scooting and swimming to reading and listening to music. A few parents mentioned that a limited attention span could influence the activities their child enjoyed.

"He is very sweet and funny, with a huge heart. He is very warm and engaging with people he knows, but tends to be shy when first meeting people. He has some very good friends but struggles with initiating new social interactions. When he does meet new people he engages more easily with adults initially than other children." - dup 5q14.3 (including *MEF2C*), 10 years

"He is a very happy child and enjoys socialising, especially with family members. He enjoys being active - running, jumping and climbing - and watching TV, but has very little attention span." - dup 5q14.3q15 (including *MEF2C*)

"She is a happy, loving child who is quite sensitive. She likes being at home in her own environment best. She enjoys company, but doesn't know how to join in or start a conversation. This can make her shy or frustrated, which then leads to a breakdown." - 5q14.3q15 (including *MEF2C*), 13 years

"He is a sociable, bubbly and caring little chap. If he thinks he's hurt me he will give me a cuddle (or even cry himself), and once got a tissue to wipe my eyes when I cried." - dup 5q14.3q23.1 (not including *MEF2C*), 2 years

"She is very sociable, loving and affectionate. She is also physical and very flitty and goes from being happy to distraught in a second. She craves attention wherever she goes. Hates changes to routine, and needs to move constantly." - dup 5q14.3q31.1 (not including *MEF2C*), 4 years

"Charming, sweet-natured and mostly happy unless he can't communicate his needs. He has an amazing, funny personality; he is goofy and has a contagious laugh. He is very affectionate, loves the attention from people and loves to give kisses. He has no interest in toys and does not know how to self-entertain, but he loves music and books." - dup 5q11.1q14.1 (not including *MEF2C*), 7 years

"Challenging" behaviours

Against this usually loving, sunny disposition and numerous positive traits, children could experience sudden "mood swings" and "challenging behaviours". Very rarely, children could demonstrate aggressive or self-injurious behaviours, such as scratching and skin picking (Unique).

Difficulties in communicating needs, shyness, anxiety or recognising differences between them and their siblings or peers, could lead to frustration. 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. Where possible, early access to advice and therapy is recommended to help those families who find themselves in difficulties with their child's behaviour (*see Unique*'s guide to Behaviours).

" He can be very shy and resistant to new situations, based on his anxiety. At times he can be very irritable, defiant and difficult to reason with. He can be very sweet one minute and very pouty and seemingly angry the next. He is very comfortable when he knows people but extremely shy at other people's homes or in new settings. " - dup 5q14.3 (including *MEF2C*), 10 years

" He is a very happy child, but does get frustrated sometimes, especially in larger groups with loud noises. " - dup 5q14.3q15 (including *MEF2C*)

"Occasionally hits out unexpectedly, kicks etc. and we have recently realised that it happens when she is given a choice and can not make a decision or resolve the situation cognitively. She doesn't know or can't say the right thing or react appropriately - obviously this has become more apparent as she has got older. " - dup 5q14.3q15 (including *MEF2C*), 13 years

" Shy outside the home but interacts well at home, although she does get frustrated with her more able siblings. Picks at her healthy skin and scabs but exhibits no other self-injurious behaviour. No signs of hand flapping or aggression. " - dup 5q13.3q14.3 (including *MEF2C*)

" Goes from happy to distraught in a second. She has severe separation anxiety and can be very physical with others. Sometimes hurts herself and others to gain attention. She is very sociable, but is just starting to become aware that she is different. Severe speech and global developmental delay, which may be challenging over the next year as she starts school. " - dup 5q14.3q31.1 (not including *MEF2C*), 4 years

" He is sweet-natured but can be good at finding a behaviour that frustrates me and doing it repetitively. He has had some self-injurious behaviour, but it has not been severe and at this age it is very minimal, if not absent." - dup 5q11.1q14.1 (not including *MEF2C*), 7 years

Social, emotional & anxiety disorders

Some children with a 5q14.1 duplication have received a diagnosis for a specific social, emotional or anxiety disorder, including an autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). ASDs include autism and Asperger's disorder and are 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. Children with ADHD demonstrate a range of behaviours, including hyperactivity, inattentiveness and impulsiveness, which 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. The reasons for such behaviour are not always understood but are thought to have a neurological basis.

At least five cases of autism in individuals with a tiny 5q14.1 duplication have been recorded in DECIPHER, while a few others had behavioural concerns or difficulties with social situations (DECIPHER). One *Unique* member with a tiny 5q14.1 duplication also received an autism diagnosis, and a seven-year-old boy with a 5q11.1q14.1 duplication was diagnosed with autism and ADHD (Unique). The *HOMER1* gene located in 5q14.1 has been identified as an autism risk gene (Kelleher; 2012; Banerjee 2016).

In the medical literature there were no reported cases of ASDs or ADHD associated with 5q14.3 duplications including *MEF2C*, although one child had pronounced anxiety in social situations as a four-year-old, but was markedly less anxious with greater sociability by the age of six. In DECIPHER there were two cases of individuals with autism with a duplication involving only 5q14.3, only one including *MEF2C.* Only one *Unqiue* member with a duplication including 5q14.3 had a diagnosis of ADHD and there were no cases of autism reported by parents (Novara 2013; 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 was diagnosed with autism when he was two years old." - dup 5q14.1 (not including *MEF2C*)

"He has been diagnosed with autism. He is always on the go, very active and never stops until it is time to sleep. He doesn't know how to interact with kids

but he wants to, although he didn't have any interest in kids until about age five or six." - dup 5q11.1q14.1 (not including *MEF2C*), 7 years

"He was diagnosed with ADHD when he was seven years old. He can be irritable and disruptive due to change or things he doesn't understand in school. He also has anxiety and is on medication for both." - dup 5q14.3 (including *MEF2C*), 10 years

Sleep

Many 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. For many, issues around sleep improved with age (Unique).

Where sleep has been particularly challenging, some *Unique* families with a child(ren) affected by a rare chromosome disorder 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.

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 used to have trouble falling and staying asleep but sleeps much better now, typically falling asleep easily and staying asleep." - dup 5q14.3 (including *MEF2C*), 10 years

"He is a very light sleeper and wakes throughout the night." - dup 5q14.3q15 (including *MEF2C*)

"She sleeps well but calls down lots before going to sleep. For many years she slept with us and now, although in her own bed, calls out all the time to check we are there and comes down in the night to our room. She will go back to her bed but then appears again. A difficult reality for us all." - dup 5q14.3q15 (including *MEF2C*), 13 years

"Normal sleep pattern but gets tired more easily than do her sibs." - dup 5q13.3q14.3 (including *MEF2C*)

"We started using Melatonin at three-and-a-half years due to her taking three hours to get to sleep, then being wide awake from one 'til five am. It worked amazingly well and has made such a difference. I think her attention levels have increased since she started sleeping better." - dup 5q14.3q31.1 (not including *MEF2C*), 4 years

"He did have episodes when he was younger in which he would wake up in the middle of the night and never go back to sleep. At age seven, he sleeps very well and, as of recently, no longer wakes in the middle of the night to get in bed with me." - dup 5q11.1q14.1 (not including *MEF2C*), 7 years

Puberty

There is extremely limited information available about puberty in children with a 5q14 duplication. One 13-year-old girl with a 5q14.3 duplication including *MEF2C* appeared to be going through puberty as expected, while a 10-year-old boy was showing the first signs of puberty. Some families of children with chromosome disorders and behavioural or learning difficulties are particularly concerned at their daughters' ability to cope with menstruation, and for some discussing menstrual regulation options with a paediatrician may be beneficial. *Unique*'s guide to "Puberty" provides helpful information.

Medical concerns

General well being

The majority of *Unique* families described their child's general state of health as "good" or "very healthy". However, most parents did tell us that their child was susceptible to ear infections, colds and other respiratory infections. A few children have on-going health conditions, including recurrent chest infections, asthma and seizures. A four-year-old girl with a large 5q14.3q31.1 duplication seemed to be particularly affected (Unique).

Head shape

Smaller head size (microcephaly) is one of the most consistent features of 5q14.3 duplications and has been reported in the medical literature to be associated with upregulation of the *MEF2C* gene. At least four *Unique* children, three children in the medical literature and one case in DECIPHER with a duplication including *MEF2C* had microcephaly.

A four-year-old girl with a large 5q14.3q31.1 duplication not including *MEF2C* also had a small head, as did a boy recorded in DECIPHER with a 5q14.3q15 duplication not including *MEF2C*. A two-year-old *Unique* boy with a 5q14.3q23.1 duplication not including *MEF2C* had a small but proportionate head, although his skull was slightly flattened.

Only one child with a tiny 5q14.1 microduplication reported in DECIPHER had microcephaly, and there were no further reports of a small head associated with 5q14.1 duplications (Le Meur 2010; Novara 2013; Yuay 2019; DECIPHER; Unique).

Eyes & Vision

Problems with vision, both short- or long-sight, were reported for several children with 5q14.3 duplications including *MEF2C*. A girl or woman in

DECIPHER with a large 5q13.3q14.3 had a structural anomaly affecting the retina of the eye. Two children 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 can work well to correct a squint, but for some a surgical operation may be recommended. One child developed a "lazy eye" (amblyopia), which can be a consequence of a constant squint in one eye (Novara 2013; Unique).

A four-year-old *Unique* girl with a large 5q14.3q31.1 duplication not including *MEF2C* also had problems with peripheral vision, causing her to trip over regularly. A two-year-old *Unique* boy with a 5q14.3q23.1 duplication not including *MEF2C* was found to have Duane's syndrome in both eyes (a problem with turning the eye) due to the absence of the 6th cranial nerve that usually sends signals to a small muscle that attaches to the outer side of your eye, a slight drooping (ptosis) of his right eyelid and temporarily blocked tear ducts that resolved by 8 weeks.

A seven-year-old *Unique* boy with a 5q11.1q14.1 not including *MEF2C* was long-sighted and had nystagmus (uncontrolled eye movements).

Seizures

Seizures are caused by a change in electrical activity in the brain. Depending on the part(s) of the brain affected, symptoms vary but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Age of onset can vary considerably, while seizures may be isolated to a single incident or occur more regularly.

Electroencephalograph (EEG) and video telemetry (video EEG) are medical tests that can be used to measure and record the electrical activity of the brain and are tools that, when used alongside other tests, can help diagnose the type of seizure experienced.

Seizure types include:

Febrile seizure Episodes only occur when the child has a high temperature.

Absence seizure A change in behaviour as if the child 'switches off', sometimes with staring, eyelid flickering or lip smacking. Absences are very brief often lasting less than half a minute.

Atypical absence seizure Child may appear confused and unresponsive for minutes, very different from a typical absence seizure.

Infantile spasm Type of seizure usually occurring in clusters in babies between 3-10 months. Seen most often when a baby wakes and may be obvious, or subtle.

Generalised tonic clonic At the onset of a seizure, the abnormal electrical activity involves both sides of the brain. The seizure involves a phase of stiffening followed by jerking.

Myoclonic Generalised seizure Involving jerky or shock-like contraction of different muscles anywhere in the body but usually the arms or legs. Each myoclonic seizure lasts for a fraction of a second or a second at most.

Myotonic Seizure involving stiffening of the muscles.

Myoclonic-atonic Seizure involving jerky or shock-like contraction of muscles, followed by a loss of tone so someone standing up falls to the ground.

Seizures are not thought to be a common feature of 5q14 duplications including *MEF2C*. However, a girl in the medical literature (a single febrile seizure), two cases in DECIPHER (one generalised tonic-clonic seizures; one generalised myoclonic seizures and generalized tonic-clonic seizures) and two *Unique* children, had experienced seizures. A 9-year-old girl with a balanced translocation resulting in upregulation of the *MEF2C* gene had also experienced a febrile seizure (Novara 2013; Yuay 2019; DECIPHER; Unique).

Two further cases of seizures/epilepsy in a female and male in DECIPHER with 5q14.3 duplications not including *MEF2C* have also been reported. A four-year-old *Unique* girl with a large q14.3q31.1 duplication not including *MEF2C* experienced several types of seizure from the age of three years.

There are only two reports in DECIPHER of seizures (generalised tonic; epilepsy) associated with tiny 5q14.1 duplications.

“ She had one small epilepsy incident when she was 10 years old. Test results indicate that it could happen again, although it hasn't so far. ” - dup 5q14.3q15 (including *MEF2C*), 13 years

“ He was recently diagnosed with seizures. He had had symptoms since he was 8 years old with no confirmed diagnosis. Symptoms include staring spells, coupled with twitching in the legs and pulling in of the right arm to the body and falling to ground. Limbs go limp briefly afterwards. He started on Kepra twice daily in hospital. Have not seen any falling since and minimal staring episodes. Previous EEGs when he was younger (at two and six years) were "normal". Stress seems to bring seizures on more and doctors confirmed they lower the threshold for having a seizure. ” - dup 5q14.3 (including *MEF2C*), 10 years

"She had her first tonic clonic seizure at the age of three and developed focal seizures and tics six month later. These have gone from 100 a day to one or two a day. She is on 6ml Carbomazepine twice daily." - dup 5q14.3q31.1 (not including *MEF2C*), 4 years

Brain

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. Under MRI, a number anomalies of the brain have been reported in association with 5q14 duplications, but many were mild and many individuals appear to be unaffected.

For duplications including the *MEF2C* gene, these included two cases in the medical literature of mild ventriculomegaly (the fluid-filled spaces of the brain are larger than normal). Two cases of partial agenesis of the corpus callosum found in ultrasound scans on twins with a 5q14.3 duplication were also reported. The corpus callosum is a band of nerve fibres joining the left and right sides of the brain. It can be missing altogether (agenesis) (ACC), or it can be thin, short and underdeveloped (hypoplastic) (HCC). The effects vary, but both intellectual and physical development may be impaired. There were also three cases in the medical literature where MRI findings were normal. A *Unique* boy had a cyst (fluid-filled sac) on the pituitary gland and an arachnoid cyst (fluid filled sac located in the brain). A case of periventricular heterotopia (a disorder characterised by abnormal clumps of nerve cells around fluid-filled cavities near the centre of the brain) in DECIPHER with a tiny 5q14.3 duplication was also reported (Le Meur 2010; Novara 2013; Cesaretti 2016; Yuay 2019; DECIPHER; Unique).

A two-year-old *Unique* boy with a 5q14.3q23.1 not including *MEF2C* was missing the 6th cranial nerve to the eyes (*see* Eyes & Vision).

Only two incidents of brain anomalies have been reported in association with a 5q14.1 duplication. A seven-year-old *Unique* boy with a 5q11.1q14.1 had a Chiari malformation type 1, where the lower part of the cerebellum extends below the large hole at the base of the skull, without involving the brainstem. In DECIPHER, a female with a tiny 5q14.1 duplication had cerebellar atrophy (loss of nerve cells in the brain and the connections between them) and cortical dysplasia (when the top layer of the brain does not form properly).

"A brain MRI identified a cyst on the pituitary and an arachnoid cyst. Both considered to be ancillary (secondary) findings and have been monitored via MRI regularly since. The cysts are growing with him. Also do yearly endocrinology labs to monitor hormone levels based on the pituitary cyst. Has twice-yearly check ups with the ophthalmologist for early monitoring." - dup 5q14.3 (including *MEF2C*), 10 years

Kidneys and urinary tract infections

A baby with a 5q14.3 duplication including *MEF2C* experienced frequent urinary tract infections (UTIs). These were thought to be related to buried penis syndrome (where the penis is partially or completely covered by skin), which was corrected surgically. Preventative antibiotics were extremely effective and prevented further UTIs. One child with a duplication including *MEF2C* had kidney (urethral) reflux (where urine flows upwards from the bladder back up to the kidney, potentially damaging the kidneys and leading to frequent UTIs).

A child with a 5q11.1q14.1 duplication not including *MEF2C* experienced kidney reflux and had a very large bladder.

Ears & Hearing

Regardless of the size of the duplication, frequent ear infections were common. These can sometimes lead to a build-up of fluid in the middle ear, called glue ear. Glue ear usually resolves as children get older, when the ear tubes widen and become more vertical resulting in improved drainage of the middle ear.

However, persistent fluid in the middle ear and glue ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, parental concerns should be acted on early and home- or school-based therapy provided. While glue ear persists, a number of children have needed a grommet (a small ventilation tube) inserted into the eardrum, although hearing aids have not been necessary.

“ He experienced chronic ear infections between the ages of two and five years, which required four sets of grommets. Some of the ear infections temporarily impacted hearing, but that has been resolved. ” - dup 5q14.3, 10 years

Hands & Feet

Children with a 5q14 duplication often had minor anomalies of the hands and feet. Most common among these were flat feet (pes planus), broad toes or thumbs and fingers or toes that curved inward (clinodactyly). Among *Unique* members were individual cases of long toes, a “sandal gap” between the big toe and second toe, “puffy” feet and under-developed nails (Novara 2013; Yuay 2019; Unique).

Eczema

Several children with a 5q14.3 duplication including *MEF2C* had eczema, where the skin to become red, itchy and inflamed. Two children with duplications involving 5q14 but not *MEF2C* also had eczema. Your doctor should be able to recommend self-care techniques, emollients and other treatments that may help to relieve symptoms (Unique).

"Has eczema on backs of arms and sometimes on the face or legs."
- dup 5q14.3, including *MEF2C*, 10 years

"Dry skin with eczema around her eyes and in the limb flexures."
- dup 5q13.3q14.3, including *MEF2C*

Heart

MEF2C has a role in heart development but so far there is only one report in the medical literature of a heart condition associated with a duplication including *MEF2C*, where prenatal ultrasound revealed a baby with biventricular hypertrophy and a problem with the tricuspid valve. No *Unique* member or cases in DECIPHER reported having a heart problem (Cesaretti 2016; DECIPHER; Unique).

DECIPHER lists a case of a bicuspid aortic valve associated with a tiny 5q14.3 duplication not including *MEF2C.*

One *Unique* baby with a large (~43Mb) duplication spanning 5q14.3 to 5q31.1 (not including *MEF2C* and only including part of 5q14.3) was born with pulmonary stenosis, which resolved naturally, and a persistent ductus arteriosus (PDA) that was closed through surgery at 22 months.

"I feel that after she had heart surgery, the lights went on behind her eyes. She lost the vacant gaze and started to interact with the world." - dup 5q14.3q31.1 (not including *MEF2C*), 4 years, UK

Teeth

Dental problems are very common in children with chromosome disorders and a high standard of dental care is important. Interestingly, dental problems don't appear to be common among children with 5q14 duplications, with only two reports of over-crowding and, conversely, one of wide gaps between the teeth (Unique).

Other medical concerns (*Unique* members)

Prominent thoracic cage: one case (dup 5q13.3q14.3 including *MEF2C*)

Umbilical hernia: one case (dup 5q11.1q14.1 not including *MEF2C*)

A high/arched palate: two cases (dup 5q13.3q14.3 including *MEF2C*; dup 5q11.1q14.1 not including *MEF2C*)

Excessive hair growth: one case (dup 5q14q31 not including *MEF2C*)

Tight ankles: one case (dup 5q14 including *MEF2C*)

Hypermobile joints: one case (dup 5q14.3q31.1 not including *MEF2C*)

Keratosis pilaris: one case (dup 5q14.3q31.1 not including *MEF2C*)

Families say...

❝ We are very involved at school and at home to ensure all the tools, therapies, etc. are provided. We also try many different activities e.g. sports and music, to find what our son enjoys and excels at. Do not give up hope, we have seen incredible progress in our son. ❞

❝ Try and watch your child and let their needs guide you. Meet with other parents who understand and stay strong for your child. ❞

❝ It is a roller-coaster journey with a lot of unknowns. We all want what is best for our kids and it is so hard when you cannot predict their future. The My Support Plan and EHCP have really helped bring everyone together and look at her needs as a whole. ❞

❝ My advice to other families is to not get so caught up on the outcome for the future. Focus on getting support for the whole family. Get respite time as often as you can, especially for date nights with your spouse. When you learn to accept your situation, help those that are still learning. ❞

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)

Inform Network Support

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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.

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Rare Chromosome Disorder Support Group Charity Number 1110661

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