

Inform Network Support



Understanding Chromosome & Gene Disorders

Rare Chromosome Disorder Support Group

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

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

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



Understanding Chromosome & Gene Disorders

5q35 duplications



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 2019 and reviewed by Dr Roberto Ciccone, Department of Molecular Medicine, University of Pavia, Italy.

Copyright © Unique 2020

Rare Chromosome Disorder Support Group Charity Number 1110661

Registered in England and Wales Company Number 5460413

rarechromo.org

5q35 duplications

A chromosome **5q35 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 5q35 duplication is extremely 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.

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 (usually 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.



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

Facebook Groups

Reversed Sotos Syndrome (73) - <https://www.facebook.com/groups/313154342038158/> - For people or parents of children with "reversed Sotos syndrome", to share experiences and information.

Chromosome 5 duplication (176) - <https://www.facebook.com/groups/1548614302021901/> - This group was created in hopes of connecting with others who have children or are themselves affected by this rare duplication in chromosome 5.

(Number of members as at Feb 2020 in brackets)

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](https://doi.org/10/1016/j.ajhg.2009.03.010)]

singing so much she was allowed in. She also enjoys the social element of the choir. She enjoys the fact that most of the members are older and she picks up a lot from them (in a positive way). She's always liked being with adults, rather than with children. Now that she is a teenager she is officially allowed to be with grown-ups. As she is a very observant person she can pick up a lot from just watching. Many teachers etc. underestimate that. ” - dup 5q35.2q35.3, 13 years

Families say...

“ My advice is to take it one day at a time! Don't compare your child to others; focus on what he or she can do instead of what they cannot. Everything will, and eventually does, get easier. ”

“ When we first got the diagnosis from the paediatrician, all I felt was relief; that it has not been my fault as a mother. My advice would be to never stop talking to each other and get help from a professional if needed. The most important thing is to find other parents of a child with a genetic condition. So the best thing is to join *Unique!* I set up a blog just after we got the diagnosis and a Facebook group (see page 35). I met with one family in London just days after they got the diagnosis, and this helped us both so much! So I would say that connecting is key. ”



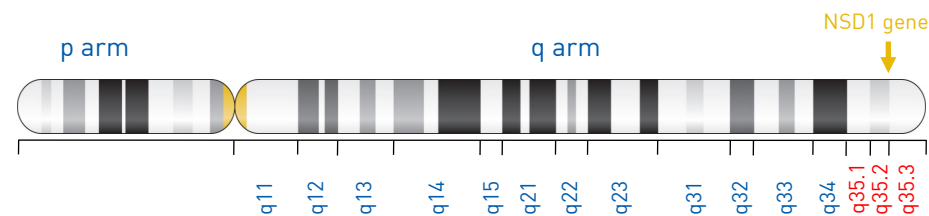
“ Be an advocate for your child and fight for what they can get! ”

“ See your child as someone wonderful and unique and get as much family support as you can. Explain the condition to their siblings/cousins as children can be wonderfully kind. ”

“ Remember that two kids with an identical diagnosis may be very different, in the same way that two “typically”-developing kids will be completely different. Parents are the experts in their child's health and may need to fight for their well-being. ”

“ The advice I would give is don't worry about not knowing what the future holds. Our geneticist told us not to let her diagnosis overwhelm us but to look at our daughter and SEE her. As time goes on I don't see her diagnosis at all, but only her. She is not a medical condition, she is herself and we couldn't love her more. ”

Chromosome 5



People with a 5q35 duplication have one normal chromosome 5, but the other chromosome 5 has an extra piece of chromosomal material from band q35 of the long arm (marked in red).

Chromosomal changes

At fertilisation, a sperm and egg cell join to form a single cell. Changes to the structure of chromosomes often occur during the cell divisions that lead to the creation of egg or sperm cells.

During this complicated process, chromosomes arrange themselves in their 23 pairs, with pairs lying alongside each other, apart from the sex chromosomes X and Y which attach to each other at both ends. The chromosome pairs ‘recognise’ each other because they are similar. Segments of DNA are then exchanged in a process known as crossing-over (**recombination**) and the chromosomes are held together at the crossing points (known as **chiasmata**).

However, where the DNA of the chromosome is repeated at close intervals “mistakes” may occur, leading to parts of a chromosome(s) being lost, duplicated and/or becoming rearranged. Many of the chromosomal rearrangements involving chromosome 5q35 are due to the presence of two **low copy repeats (LCR)** in the 5q35 band. Most of the DNA that makes up chromosome 5q is present as a unique sequence, but the presence of these LCRs results in two sections where the DNA sequence is repeated at close intervals. These repeated sections are in a more proximal repeat in 5q35.2 called **Sos-PREP** and a more distal repeat in 5q35.3 called **Sos-DREP**. The

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>. Twelve *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.

presence of Sos-PREP and Sos-DREP also means the replication machinery is more likely to “trip up” during the production of the sperm or egg cell resulting in chromosomal rearrangements like duplications and deletions.

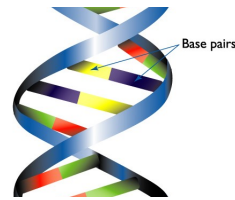
The region between Sos-PREP and Sos-DREP contains the *NSD1* gene (see blue box). Having an extra copy of the *NSD1* gene is thought to play a crucial role in some of the features associated with 5q35 duplications (Franco 2010; Dikow 2013; Rosenfeld 2013).

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 many duplications involving 5q35, are called **microduplications** (microduplications and microdeletions can vary from a few kilobases to 10 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.

The more commonly used test nowadays is called **chromosomal microarray (CMA)** and



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

The *NSD1* gene

Location: chromosome 5q35.3 (176,560,026-176,727,216 (GRCh37/hg19))

The *NSD1* gene codes for a protein called nuclear receptor SET domain-containing protein 1. This protein regulates the expression of another gene called *APC2*, which participates in brain development, as well as a number of other genes required for the normal development of the heart, skeleton and kidneys.

The presence of an extra copy (duplication) of the *NSD1* gene is believed to be responsible for many of the features associated with 5q35 duplications, while the absence (deletion) of the *NSD1* gene is associated with Sotos syndrome 1 (see page 10, Sotos syndrome-1 (SS) & “reversed Sotos syndrome”). Other genes located in 5q35 are likely to contribute to the features associated with 5q35 duplication, although the implications of a duplication of other individual genes is not yet known (Almurieghi 2015; Tatton-Brown 2005; Dikow 2013; Reis 2017).

Puberty generally seems to have proceeded as expected with no real cause for concern, although mood swings could be hard to handle (Dikow 2013; Novara 2014; Unique).

“ I can honestly say she embraces it! I have not seen another child enjoying the change of their body so much as her. She notices every change and talks about it - very positively. ” - dup 5q35.2q35.3, 13 years

“ The experience has been OK, except for mood swings and she can't manage her periods. ” - dup 5q35.2q35.3, 16 years

“ She had a huge growth spurt and went from age 7 to age 10-12 clothes in two months. She developed breasts and had two periods before her ninth birthday. ” - dup 5q35.3

Growing up/Adulthood

At the time of writing, *Unique* had only a few adult and teenage members with a 5q35 duplication. One parent was found to have a 5q35.3 duplication only after his first child was found to carry the same duplication; similarly, another parent was found to have the same duplication as her son following his diagnosis (see comments below).

The DECIPHER database has cases of seemingly unaffected parents who passed on a 5q35 duplication to their child.

In the medical literature, a 39-year-old woman with a 1.6Mb 5q35.2q35.3 microduplication had a presumed mild LD. Her three teenage children had all inherited the duplication, had the features of 5q35 duplications and were fostered from a young age. A 35-year-old woman with a 1.5 Mb 5q35.2q35.3 had a mild LD, noticeably short stature and mild dysmorphic facial features. Her 9-year-old son had inherited the microduplication and also showed similar, typical characteristics (Dikow 2013; Unique).

Experiences of adulthood are likely to vary considerably and will depend on many factors. These include the level of any LD/ID, possible on-going medical concerns and improvements in early intervention.

“ It was quite a shock to hear of my child's duplication and even more so to know it has come from me. It explains a lot, as I have a horse shoe-shaped kidney and was a late developer. ” - dup 5q35.3, parent

“ Some executive functioning issues and autistic traits, but no social or communication issues. ” - dup 5q35.3, parent

“ Whilst she is chronologically 16-years-old, mentally she is maybe 8-years-old. ” - dup 5q35.2q35.3, 16 years

“ She loves singing and is member of a Youth Choir. She joined very young at age 11. The choir officially accepts children from age 12, but they loved her

■ Limbs & Joints

Loose, hypermobile joints affected 5/11 *Unique* members with a 5q35 duplication in the 2018 survey.

Hypermobility often 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 boy in the literature with a 5q35.3qter duplication was born with arms that were significantly shortened due to the absence of the shorter (radius) bone and underdevelopment and bowing of the longer (ulna) bone in both his forearms (bilateral radial aplasia), as well as absent thumbs (Jamsheer 2013; *Unique*).

■ Other medical concerns

Kidney reflux (leading to frequent urinary tract infections): one case *Unique* (5q35.2q35.3)

Ataxia: two cases DECIPHER (5q35.3)

Hyposalivation: one case *Unique* (5q35.2q35.3)

Hypospadias (where the hole usually sited at the end of the penis is on the underside instead) & **cryptorchidism** (undescended testicle(s)), corrected by surgery: one case *Unique* (5q35.2q35.3)

Excessive hair growth: one case *Unique* (5q35.2q35.3)

Alopecia (hair loss from some/all of the body): one case *Unique* (5q35.2q35.3)

A high palate: one case *Unique* (5q35.1q35.3)

Cleft lip/palate: two cases DECIPHER (5q35)

Anomalies in thyroid hormone levels: two (unconfirmed) cases *Unique* (5q35.2q35.3; 5q35.3)

Puberty

Puberty can be a challenging time for any family. The information we have relating to puberty and 5q35 duplications is limited, but there appears to be a trend towards delayed puberty in those with a 5q35.2q25.3 duplication including *NSD1*. Among *Unique* families, two girls went through puberty at the expected age or a little late, while in the medical literature a 13.5-year-old girl showed no signs of puberty and another girl started her periods at 15 years. A girl with a 5q35.3 duplication appeared to have entered puberty early (precocious puberty).

allows genomic DNA to be analysed in greater detail. An array test can detect very small duplications and 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 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 (*see* **Mosaicism**).

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 5q35 duplication might have results that look like one of these examples:

46,XY,dup(5)(q35.1q35.3)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. **(q35.1q35.3)** shows the part of the chromosome that is duplicated; in this case, there is a gain of a chromosome segment from q35.1 to q35.3. 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.

arr[hg19] 5q35.2q35.3(175559325_177422730)x3pat This result shows that the analysis used microarray technology (**arr**). The analysis revealed a DNA anomaly involving **5q35.2** to **5q35.3**. 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 **175559325** and **177422730** (by taking the first number from the second, you can work out that this is 1,863,405 base pairs, or **1.86 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)). The anomaly has been inherited from the father (**pat**).

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 hg18, 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.

mos dup(5)(q35.2q35.3)[11]/46,XX[22] 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-three cells have been tested. Eleven ([11]) cells had a duplication of chromosome 5 (**dup(5)**). (**q35.2q35.3**) shows the part of the chromosome that is duplicated; in this case, there is a gain of a chromosome segment from q35.2 to q35.3. Twenty-two [22] 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 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 very 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. Even siblings with the same parents and the same duplication can have different outcomes. A child's other genes, environment and unique personality 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.

small ventilation tube) inserted into the eardrum.

One baby in the medical literature had a hearing impairment in their left ear when tested soon after birth (Jamsheer 2013; Unique).

“Until she was she was 42 months, she had frequent ear infections. Grommets were placed at that age and since then she hasn't had a problem with ear infections. We saw the ear, nose and throat (ENT) doctor until she was six for check-ups.” - dup 5q35.2q35.3, 13 years

■ Hernias

Three *Unique* babies and one baby in the medical literature with 5q35.2q35.3 duplications were born with a hernia, where an organ or fatty tissue pushes through a weak spot in a surrounding muscle or tissue. In all the *Unique* cases these were umbilical (at or near the belly button), while the case in the literature was inguinal (inner groin). Hernias may heal naturally without the need for treatment, but in the majority of cases surgical repair is usually required (Chen 2006; Unique).

■ Hands & Feet

Rarely, children had minor anomalies of the hands and feet. Most common among these were fingers or toes that were unusually short (brachydactyly), or occasionally long and tapering (arachnodactyly) or curved inward (clinodactyly). Two children with a 5q35.3 duplication had flat feet (pes planus), while two children with a 5q35.2q35.3 duplication had a “sandal gap” between their big toe and second toe. Individual children had other conditions such as fused fingers (syndactyly) and, in the most severe case, absent thumbs (Dikow 2013; Jamsheer 2013; Novara 2014; Unique).

■ Teeth

Dental problems are very common in children with chromosome disorders, including among *Unique* members with a 5q35 duplication (9/12 *Unique* survey).

Most often, *Unique* children were prone to dental decay (caries); late teething; missing or unusually small teeth; and abnormally thin and weak enamel (enamel hypoplasia). There were also individual cases of impacted teeth, over-crowding and, conversely, wide gaps between the teeth.

A high standard of dental care is extremely important to minimise damage by decay and erosion. Children and adults may also benefit from specialist hospital dental services (Unique).

“Weak enamel and subsequently dental caries in the milk teeth resulted in four crowns being placed and four teeth pulled. Several teeth needed fillings. The decay happened very fast - while we were on the waiting list to see a children's dentist. Happily, the adult teeth are fine and she doesn't have any issues.” - dup 5q35.2q35.3, 13 years

■ Heart

Heart conditions are uncommon and have only been reported for a few individuals, with no particular defect associated with 5q35 duplications.

One five-year-old *Unique* girl with a 5q35.1q35.3 duplication was born with an atrial septal defect (ASD) (a “hole” between the upper and lower heart chambers), and was later diagnosed with a mild case of pulmonary valve stenosis (a pulmonary valve in the heart is thickened or fused so that it doesn’t open fully, affecting the flow of blood and resulting in the heart having to work too hard). Another four-year-old *Unique* boy with a 5q25.2q35.3 duplication had two ventricular septal defects (VSD) (where 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), which closed spontaneously and did not require treatment.

A 10-year-old boy with a 5q35.3 duplication had a heart murmur. In the *Unique* database there is a record of a baby with a 5q35 duplication who was born with an aortic coarctation (a narrowing of the major blood vessel (aorta) that carries blood from the heart to the body), requiring open heart surgery at two-days-old.

The medical literature reports a case of a four-year-old boy with persistent foramen ovale (PFO) (where the opening between the two upper chambers of the heart that is open during pregnancy does not close as expected soon after birth) that didn’t affect blood flow. Similarly, a 9.5-year-old boy with a 5q35.2qter duplication had PFO, which had virtually disappeared by two years, and dextrocardia and dextroversion (the heart is positioned to the right instead of the left of the chest, without the usual rotation associated with dextrocardia, so it isn’t an exact mirror image) (Unique, Reis 2017; Jamsheer 2013).

In DECIPHER there were individual cases of an under-developed left-side of the heart (5q35.2); pulmonary stenosis (5q35.2q35.3); VSD (5q35.3); and an unspecified abnormality of the cardiovascular system (5q35.3).

■ Ears & Hearing

A few babies and young children (3/12 *Unique* survey) suffered from frequent ear infections. These can sometimes lead to a build-up of sticky 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. Therefore, any hearing loss caused by glue ear is usually temporary.

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, while glue ear persists, many children will need a grommet (a

Mosaicism

In a few people, the cells containing the 5q duplication chromosome material may exist alongside cells with a normal chromosome number and arrangement. This situation, known as **mosaicism**, typically arises after fertilisation and can lessen the impact of the duplication. In 2019, *Unique* had two members with confirmed 5q35 duplication mosaicism, one involving 5q35 alone and one spanning 5q33 to 5qter. DECIPHER (*see How common are 5q35 duplications?*) lists one person with a 5q35.2 duplication that was maternally inherited, where there was mosaicism in the mother.

The proportion of 5q duplication cells 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 the medical literature for other rare chromosome disorders, the outcome of the condition was in some cases milder.

How common are 5q35 duplications?

It is difficult to estimate the prevalence of 5q35 duplications since many people will not have been diagnosed, and many of those who are diagnosed are not reported. However, at least 31 people with a 5q35 microduplication including the *NSD1* gene have been reported in detail in the medical literature (Chenet 2006; Kirchhoff 2007; Franco 2010; Zhang 2011; Dikow 2013; Rosenfeld 2013; Zilina 2013; Novara 2014; Reis 2017).

At the time of writing, there were also 46 cases with a 5q35 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 35*)). Of these 46 individuals, two had a microduplication involving 5q35.1 alone; seven involving 5q35.2 alone; 8 involving 5q35.2 and 35.3; 27 involving 5q35.3 alone; and one case each of a duplication spanning 5q35.1q35.2 and 5q35.1q35.3. There were many other cases where an individual had a 5q35 duplication in addition to recorded genomic variants involving other bands of chromosome 5 or another chromosome(s) e.g. other duplications or deletions.

Unique had 29 family members worldwide with a duplication involving 5q35 alone. Of these, 21 cases included the *NSD1* gene. One member had a microduplication involving 5q35.1 alone; two involving 5q35.2 alone; 12 involving 5q 35.2 and 35.3; six involving 5q35.3 only; five spanning 5q35.1 to 5q35.3; and three cases where the exact 5q35 duplication was not specified. In addition, there were individual members with duplications spanning 5q33.2q35.1, 5q33.2q35.3, 5q33qter (mosaic) and a duplication of the whole of the 5q arm.

Note: As with many cases in DECIPHER, some *Unique* members have a 5q duplication alongside another chromosomal anomaly(ies). It is only those individuals with a 5q35 duplication and no other known chromosomal anomaly whose data was used to compile this guide since, for others, the reason for their clinical features may be due to the other chromosomal change(s). This guide may nonetheless be of help to explain some of their features.

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.

5q35 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. Many duplications occur in this specific region of chromosome 5 due to the presence of the two LCRs, Sos-PREP and Sos-DREP (discussed further on pages 3 & 4). Indeed, a study by Novara and colleagues found that 27 out of 30 cases of 5q35 duplications encompassing *NSD1* that were reported in the medical literature, were mediated by Sos-PREP and Sos-DREP LCRs. Of these cases, in 11 instances the origin of the duplication was not known; seven were *de novo*; six were inherited from the mother, while a further two were likely to be maternally inherited; and one was definitely not maternally inherited (Novara 2014).

Among the 29 *Unique* members with a duplication affecting 5q35 alone, in 19 cases the origin of the duplication was not specified or was unknown; six were *de novo*; two were inherited from the father, and in one case the father had a balanced translocation involving chromosomes 5 and 14; and one was inherited from the mother.

The medical literature suggests that roughly equal numbers of females (12 cases) and males (15 cases) were affected; a similar pattern was noted among *Unique* members (Novara 2014; Unique).

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 5q35 duplications. There is nothing that either parent did before, during or after pregnancy that caused the duplication.

■ Seizures

Seizures have very occasionally been reported in babies and children with 5q35 duplications. 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.

One *Unique* child, with a 5q35.2q35.3 duplication including the *NSD1* gene, experienced seizures in the new-born period, although these were controlled with medication. We also know about two children from the medical literature: one with only a partial duplication of the *NSD1* gene who had a single febrile seizure as an 18-month-old but was otherwise seizure-free, and a boy who had his first seizure as a 9-month-old. There were also two cases in DECIPHER of (unspecified) seizures, both affecting individuals with a 5q35.2 duplication not including the *NSD1* gene (Zhang 2011; Dikow 2013; Novara 2014; DECIPHER; Unique).

“ He started having seizures when he was five days old but he has been seizure-free since he was approximately five weeks old. The seizures were stabilised by anti-seizure medication. He was weaned off these medications a couple of years ago. ” - dup 5q35.2q35.3, 4 years

■ Brain

A very small minority of individuals had a brain anomaly, and such anomalies do not appear to be a consistent feature of 5q35 duplications.

These included a 16-year-old girl with a 5q35.2q35.3 duplication with ectopic neurohypophysis lying within the pituitary stalk. This rare anomaly means there will be a reduction in the amount of growth hormone and other hormones that are produced by the pituitary gland.

A child with a 5q35.1q35.3 duplication had periventricular leukomalacia (PVL), where there is damage (softening) of the white matter (inner part of the brain); gliosis (a process leading to “scars” in the central nervous system where there are areas of damage); and the fluid-filled ventricles within the brain were also somewhat larger than expected.

There is one anonymous database report in DECIPHER of cerebellar vermis hypoplasia (underdevelopment of the cerebellar vermis) in a boy with a 5q35.3 duplication. Further, a boy with a 5q35.1 duplication had absence or underdevelopment of the corpus callosum (the bundle of nerve fibres that links the brain's two hemispheres) and an enlarged cisterna magna.

Interpreting findings such as these is the job of a paediatrician or paediatric neurologist (DECIPHER; Unique).

■ Eczema

Chronic eczema that causes the skin to become red, itchy and inflamed is a recognised feature of distal 5q duplications.

As well as cases in the medical literature, 6/10 *Unique* children in the 2018 survey and a further two in the *Unique* database were affected. Your doctor should be able to recommend self-care techniques, emollients and other treatments that can help to relieve symptoms (Dikow 2013; Unique)

“ He had eczema when he was a baby. We saw a dermatologist when he was 8-months-old. It is mostly OK these days - slightly itchy at times. ” - dup 5q35.2q35.3, 4 years

■ Eyes & Vision

Children with chromosome disorders are more likely to have eyesight concerns than other children. Problems with vision and/or structural eye anomalies were reported for about two-thirds of *Unique* members with a 5q35 duplication.

Problems with vision, including long- or short-sight, were reported for four *Unique* members, although long-sightedness was more common. A *Unique* girl with a 5q35.2q35.3 duplication was diagnosed with coloboma affecting her iris, choroid, retina and optic nerve and was registered as sight-impaired.

Strabismus (a squint), where one eye or both turns inward, outward, up or down, affected four *Unique* children with at least seven further cases in the medical literature. Strabismus may be constant, or it can occur intermittently, especially when tired. Interventions like patching, exercises or glasses generally work well to correct a squint, but for some strabismus may only be corrected following a surgical operation.

A *Unique* boy with a 5q35.3 duplication, and an 8-year-old boy with a 5q35.2q35.3 duplication in the medical literature, had astigmatism, where the eyeball is rugby ball-shaped, rather than round like a football, leading to blurred vision.

A four-year-old girl with a 5q35.2q35.3 duplication had blocked tear ducts, which was corrected by surgery.

An 8-year-old boy with a 5q35.3 duplication had an inability to open his eyelids fully (ptosis), while a case of blepharophimosis, where there is a narrowing of the eye slits, was reported in DECIPHER. These conditions can cause problems with vision due to the eyelid covering the eye and reducing vision. One teenager had difficulty closing his eyelids completely.

Individual cases of nystagmus (uncontrolled eye movements) and cataracts were recorded in the medical literature (Dikow 2013; Novara 2014; DECIPHER; Unique).

Can it happen again?

Where both parents have “normal” chromosomes, it is very unlikely that another child will be born with a 5q35 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 5q35 duplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 5q35 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 5q35 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 5q35 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 three individuals with a microduplication involving 5q35.3 and a boy with a tiny 63 kb 5q35.2 microduplication. There are also other entries where a CNV involving a duplication of 5q35 is reported but its significance and/or contribution to any observed feature is unknown or uncertain. Several *Unique* members also appear to be only mildly affected by a 5q35 duplication.

Diagnosis

While one *Unique* member told us their child had received a diagnosis at one-month-old as the result of complications after birth, the majority received a diagnosis during childhood - between one and seven years - usually as the result of delayed growth, a delay in reaching developmental milestones or health concerns.

“ Genetic testing was offered at 18 months because of developmental delays. ” - dup 5q35.1q35.3

“ Our daughter was one [at diagnosis]. We had to push to have her tested and paid for it privately. She had a very small head that was identified on our 20-week scan, and confirmed at birth. She also had severe feeding

difficulties and some delayed motor skills. She didn't sit up unsupported until 11 months.” - dup 5q35.2q35.3

“ He was tested at age six due to concerns about his growth. ” - dup 5q35.3

Sotos syndrome-1 (SS) & “reversed Sotos syndrome”

The features of any genetic change can vary considerably and even siblings and parents with the same microduplication can be affected differently. While the outcome of a 5q35 microduplication will depend on the size and content of the duplication, as well as the unique genetic makeup of each person, some features are more common than others, especially among those with a duplication including the *NSD1* gene.

Deletions involving *NSD1*, or changes (mutations) to the *NSD1* gene, are linked to a well-known genomic disorder called [Sotos syndrome-1 \(SS\)](#) that affects roughly 1 in 14,000-15,000 live births worldwide.

SS is characterised by three key features: a learning disability ranging from mild to severe; pre- and post-natal generalised overgrowth, often associated with an enlarged head (macrocephaly) and advanced bone age; and characteristic facial features. Congenital heart defects, neonatal jaundice, kidney malformations, seizures and behavioural concerns are also frequently present.

More recently, a consistent set of features have emerged associated with 5q duplications that include the *NSD1* gene. Since some of these features are the opposite of those associated with deletions/mutations of *NSD1*, including a characteristic short stature and small head (microcephaly), this emerging 5q35 microduplication syndrome has sometimes been referred to as [reversed Sotos syndrome](#). However, since there aren't any consistent characteristic facial features associated with having an extra copy (duplication) of *NSD1* - unlike with deletions/mutations of *NSD1* associated with SS - and numerous other chromosome imbalances are associated with short stature and microcephaly, the label reversed Sotos syndrome is considered by some researcher to be inappropriate (Dikow 2013; Zilina 2013; Chen 2014; Novara 2014; Park 2014; Almuriekhi 2015; Reis 2017).

Common Features

When a particular set of developmental features occurs in a recognisable and consistent pattern as a result of a single cause, the condition is called a [syndrome](#). Since the features of a 5q35.2q35.3 duplications do occur in this way, a 5q35 microduplication syndrome is being increasingly recognised.

Just as “typically”-developing children can experience a number of unforeseen physical and behavioural difficulties, each person with a 5q35 duplication is unique and can have different developmental and medical concerns. However, the most likely features associated with 5q35

require me being by his side until he is comfortable.” - dup 5q35.2q35.3, 9 years

“ She is showing traits of ADHD: she is very fidgety, has difficulty keeping still and easily loses focus and concentration. This is often when other voices are around i.e. in the classroom, so don't know how much is to do with her auditory processing issue. ” - dup 5q35.2q35.3, 6 years

Sleep

Some parents of children with a 5q35 duplication told us that their child had experienced issues around sleep. These included difficulty ‘switching off’ at night, not sleeping for long periods of time and waking repeatedly in the night. Reasons for sleeping difficulties are not always well understood and are also experienced by many typically-developing children (Unique).

One 9-year-old experienced a degree of sleep apnoea (a sleep disorder that causes breathing to become shallow or stop completely during sleep) (Unique).

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 trouble transitioning to sleep and gets anxious. He often wakes up during the night. ” - dup 5q35.3, 10 years

“ From birth, we had a lot of trouble getting him to sleep. For the first 18 months we slept with him, held him in our arms, slept beside his cot. We then got help from a sleep consultant and he has slept brilliantly since. ” - dup 5q35.2q35.3, 4 years

Medical concerns

■ General well being

The majority of *Unique* families described their child's general state of health as “good” or “very healthy”.

Some parents told us that their child was more susceptible to ear infections, colds and other respiratory infections as a baby or young child, with already low weight gain adding to parental concerns if their child's appetite was affected (Unique).

“ Generally healthy with no complex medical needs. ” - dup 5q35.2q35.3, 16 years

“ If she ever got a cold her eating dropped right off. Weight gain was already enough of an issue. ” - dup 5q35.2q35.3, 6 years

important social skills. A parenting course for autism may also help parents to learn behaviour management skills, and help encourage communication and cooperative behaviour in their child, to strengthen their emotional wellbeing. Children may be prescribed medication to help with specific disorders following diagnosis - including methylphenidate (Ritalin) for ADHD, which can help with restlessness and inappropriate comments - although this may not be suitable for all.

“ He has ADHD. He is very sociable and loves other children but they often are unsure how to 'take' him. He has a tendency to be a bit pessimistic, but can be easily distracted from that - he has a bit of drama to him. Loves animals and the outdoors if we can engage him in an activity, and can play alone if he is interested. Very kinaesthetic and has just started pulling apart old cell (mobile) phones to see how they work. Loves stories and is often found sneak-reading at night. Able to self-manage toilet, showering, walking around school, meeting up at the correct place for pick up etc., but he is easily distracted and has no concept of time. He is very loving and affectionate to his family, but a bit shy around people he doesn't know. He used to go to an OT for sensory processing issues but these have improved so he no longer attends. ” - dup 5q35.2

“ At almost four years, he does not give much eye contact and displays some autistic traits. He is to be assessed for ASD at a diagnostic centre. ” - dup 5q35.2q35.3

“ She has an ASD and socialises mainly with seven-year-olds. She needs an adult to scaffold conversation for her. ” - dup 5q35.2q35.3, 16 years

“ She has been diagnosed with significant sensory processing difficulties which explain why she has fallen so behind at school, as it affects her fine motor skills. It also helps explain her anxiety (which is impacting her ability to join in) and aversion to loud noises. ” - dup 5q35.2q35.3, 5 years

“ He does have some ASD-type traits but we do not believe he has ASD as he is a very social child. He can often get fixated on objects (a lift button, automatic sliding door etc.) and can get very angry/upset/violent if you try to move him away from the object (this happens even if you give him notice to move). He would be more likely to play by himself than interact with others. He is now starting to communicate a little with other kids in preschool, but it may just be a short statement rather than open communication. He is sometimes violent towards family members and can scream repetitively if frustrated. We hope that he will be assessed by a psychologist soon. ” - dup 5q35.2q35.3, 4 years

“ He dislikes large crowds and becomes anxious. He has to know what's going on; he doesn't like sudden change. If he becomes shy he completely shuts down and will become upset very quickly. Most things he does socially

duplications, and/or those that are the most likely to make a difference to a child's health or development, are:

- Growth retardation/a short stature (duplications including *NSD1*)
- A small head (microcephaly) (duplications including *NSD1*) or unusual head shape
- Some degree of developmental delay
- Some degree of intellectual/learning disability

Other features

Many other features have been noted in the medical literature and among *Unique* members with a 5q35 duplication. A number of people with a 5q35 microduplication have a few of these features; some have almost all of them. 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 5q35 duplication and include:

- Feeding difficulties
- Speech and language delay
- Behavioural concerns
- Eczema
- Delayed bone age
- Seizures
- Problems with vision/structural eye anomalies
- Hernias
- Loose and easily extendable joints
- Frequent ear infections/glue ear, which usually resolve during childhood
- Inconsistent facial features
- An undersized jaw (micrognathia)
- Minor anomalies of the hands and feet
- Very rarely, a heart or brain anomaly
- Dental concerns

Dikow 2013; Novara 2014; DECIPHER; Unique

Pregnancy & Birth

While many pregnancies proceeded without complication, around half of *Unique* members reported having concerns during pregnancy.

Where the cause for concern was noted, most often parents reported slow

growth in the womb (intrauterine growth retardation, IUGR) (five cases - all had duplications involving the *NSD1* gene). One baby with a 5q35.3 duplication had a small hole in the heart. The vast majority of *Unique* pregnancies went to term but two babies were born premature.

“Small head circumference on scans and small growth in general; suspected IUGR, resulting in weekly scans.” - dup 5q35.2q35.3

New-born babies

Many *Unique* babies showed some signs of difficulty at birth (8/11 *Unique* survey), often related to difficulties with feeding. A few babies were jaundiced with one baby requiring phototherapy. Two babies were born with a heart condition. One baby was born with hypospadias, where the hole usually at the end of the penis is found on the underside instead. He also experienced seizures after five days. One parent described their new-born baby as “unusually inactive and placid”, a feature that may alert doctors to an underlying condition.

Growth

Most babies had a birth weight at the lower end of the “normal” range.

The average birth weight of *Unique* babies with a 5q35 duplication was 6lb 6oz (2.89kg), with a range of 4lb 2oz (1.87kg) to 7lb 2oz (3.23kg). New-born babies in the medical literature are described as short with a low birth weight (Novara 2014).

Feeding difficulties in the early months can lead to a slowing of weight gain relative to length (*see Feeding*). Among children with a duplication involving *NSD1* a growth delay was near-universal, ranging from mild to severe (8/9 *Unique* survey; 31/31 medical literature; 6/7 cases on DECIPHER (where information relating to stature was given)). *Unique* parents described their children as “short and thin”, although a few had a more “stocky” build.

The parents of two siblings with a 5q35.3 duplication (it is unclear if their duplication involves *NSD1*) told us that while one child did not experience a growth delay, the other initially appeared to be experiencing a delay but at 9-years-old had a “huge growth spurt” and was subsequently more “tall and stocky” (*Unique*). Only 3/27 cases on DECIPHER with a 5q35.3 duplication, not including the *NSD1* gene, were reported to have a short stature (DECIPHER).

No information relating to individuals with a 5q35.1 duplication alone was available.

“At seven-and-a-half years she is about 10 cm shorter than girls her age. She is very thin but her height and weight are in proportion. Her bone age is delayed by one year.” - dup 5q35.2q35.3

“She is of short stature and petite all round - small in every way, really. Her height/weight/head circumference are all on the 2nd centile. It has always

equipment but leaves easily when I ask him. When we get home, he plays music on a toy piano and then watches some TV. He eats dinner well and goes to bed quietly.

On a bad day, he can be cranky during any of these activities. He can shout and scream, refuse to do things or communicate, and say “no” to everything. He can bang on the walls and hit members of his family. To help with potential behavioural problems we did a number of parenting courses, which have helped us parent both of our kids. Thankfully, the days are mostly good and we do our best to minimise any bad behaviour.” - dup 5q35.2q35.3, 4 years

“At 11 years he has no behavioural issues. He interacts well with adults and his peers and is a very pleasant boy.” - dup 5q35.2q35.3

Social, emotional & anxiety disorders

Some children with a 5q35 duplication have received a diagnosis for a specific social, emotional or anxiety disorder, including an autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), sensory processing disorder (SPD), anxiety and depression. Others have exhibited traits associated with these disorders.

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 (Dikow 2013; Novara 2014; DECIPHER; *Unique*).

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

An occupational therapist may be able to help with some behavioural issues by giving your child tools to deal with their sensitivities, if need be. Joining a social skills group may help a child with social difficulties learn and practise

“Challenging” behaviours

Alongside many positive personality traits, many *Unique* children, regardless of the specific 5q35 duplication (10/12 survey), at times demonstrated some kind of difficult behaviour.

Children could experience sudden “mood swings”, which were also reported in the medical literature, going from being extremely active and restless to quiet and lethargic. Children could also experience difficulties with social interactions, both with adults and with other children (manifested as extreme shyness or inappropriate friendliness) and could be over-emotional. A minority of children displayed aggressive, destructive and disruptive behaviours and some have been diagnosed with specific social, emotional and anxiety disorders. It has been suggested that there may be a link between these specific disorders and 5q35 duplications and deletions, as they are also associated with Sotos syndrome-1 (see [Social, emotional & anxiety disorders](#)) [Dikow 2013; Unique].

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](#)).

“ She enjoys the company of adults and often gets on well with children younger than her - she likes to be the leader. She can be quite hyperactive and answers back, always thinking she needs the last word (mind you I’m a bit like that!). She gets very, very tired from school because she has to try so much harder - it takes a lot more concentration for her than other typically-developing kids her age. In the classroom she often relies on the teacher for support. I try to keep her food up - she often eats leftover lunchbox food on the way home from school to try to prevent a meltdown once home. ” - dup 5q35.2q35.3, 6 years

“ She is fun-loving and kind, but likes to be in control and struggles with emotions when she is not in charge. She appeared to me to be emotionally underdeveloped as she would still have massive screaming tantrums (for very little reason) up until around 9 years, but that is changing as she gets older. ” - dup 5q35.2q35.3, 9 years

“ No behaviour problems; very alert, active and affectionate. ” - dup 5q35.1q35.3

“ He is under investigation for anger problems. ” - dup 5q35.3, 8 years

“ On a good day he wakes up happy. We help him get dressed easily, he goes to crèche happily and he eats well during the day. I pick him up after crèche and he scoots to the playground. He may get fixated by a piece of playground

been hard to get and keep the weight on her. ” - dup 5q35.2q35.3, 6 years

“ Slow growth prompted the growth specialists to run genetic tests. At 10 years his growth doctor discharged him after monitoring him for three years. She has predicted that he will be short (5’ 2” to 5’ 4”); however, both his parents are short. We are monitoring his height at home on a chart she provided and this last year he has grown more than the previous three years, so we are not concerned. ” - dup 5q35.2q35.3

“ Very fine structure but in proportion. She started growth hormone treatment at age 8 years and has now had 18 months’ treatment. Her height velocity prior to treatment was 4.5cm/year. After 15 months of treatment this had increased to 12cm/year. Nobody was sure if she would respond to GH treatment before we started as it is unknown where the growth regulation is occurring; however, we are now convinced that the treatment is indeed working and it is worth trying. ” - dup 5q35.2q35.3, 9 years

“ Although he is small for his age, he is in proportion and is a good weight for his height. ” - dup 5q35.2q35.3, 4 years

Feeding

Early feeding difficulties, which were often temporary, were common among *Unique* babies.



Babies with low muscle tone (hypotonia) may find breastfeeding or bottle feeding very tiring; they may take a long time to feed or need to be fed more often. Some babies may be reluctant to feed since their sucking reflex is not developed or they find it difficult to co-ordinate sucking, swallowing and breathing. Two *Unique* babies with a dairy allergy were fed with soy milk instead.

Several 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.

[Constipation](#) is common among children with chromosome disorders and can be related to low muscle tone, little exercise, a low-bulk diet and small fluid intake. A number of babies and children with a 5q35 duplication suffered from constipation. 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.

Often feeding difficulties were mild and temporary, but sometimes they were long-lasting, required treatment or persisted into childhood (one *Unique* baby required feeding by tube, while for another tube-feeding was considered on several occasions).

Some parents mentioned that their child was a fussy eater; others struggled with textured food and chewing. Feeding for babies and children is usually a pleasurable experience. For babies with early feeding difficulties, it can become stressful and some children who have overcome their difficulties with swallowing, reflux or chewing nonetheless become food-averse. Ask your GP, health visitor, speech therapist or paediatrician about specialist feeding clinics to help avoid the 'can eat, won't eat' scenario that can then develop.

“ He became constipated before he was one-year-old. He has been on Movicol (one sachet per day) since then and it has worked well. We hope to possibly wean him off soon. He has also always had difficulties chewing. Even now, he wouldn't be great with lumps so I would mainly feed him soft-type foods that are easier to eat. ” - dup 5q35.2q35.3, 4 years

“ She would latch on OK but only fed for a few minutes. I would have to give expressed milk to top up feeds (tolerating 20ml) but she would likely vomit the lot up and developed a feeding aversion to breast and bottle. Weight gain was very poor. A naso-gastric (NG) tube was suggested at 12 months but I refused it. She had undiagnosed reflux - finally got a doctor to prescribe Omeprazole at four months and she stopped screaming at the sight of a bottle. We changed HOW we fed her at around age one (took the pressure off). It took a year but she then began to eat better. ” - dup 5q35.1q35.3, 6 years

“ Used Miralax for a few months and then switched from cow's milk to soy milk and the constipation resolved. ” - dup 5q35.1q35.3, 5 years

“ Severe allergies to milk; very low intake. At one point she was only taking one ounce of milk at each feed. Colonoscopy and endoscopy performed and reflux identified. Percutaneous endoscopic gastrostomy (PEG) almost fitted twice but just avoided it at the last minute. No solids at all until she was one, and then only smooth purees until she was two. ” - dup 5q35.2q35.3, 4 years

“ I nursed her but she gained weight only very slowly so her intake was monitored, which concluded it was sufficient. Doctors thought it would get better as soon as she was able to eat from six months onwards. A severe oral aversion prevented that, only we didn't know that back then. She only wanted breastmilk for 10 months straight. After that she slowly started showing an interest in food; food did not interest her as a baby. By seven-and-a-half years she ate very slowly, but she enjoyed her food more. ” - dup 5q35.2q35.3, 13 years

younger sister and loves to help others! She is also very adventurous and loves the outdoors, as well as music, singing, colouring, playing with dolls and swimming/play with water. ” - dup 5q35.1q35.3, 5 years

“ He is a very anxious child but is very outgoing with people who have the same interests as him. He is kind and considerate of others, but at the same time thinks the world revolves around him. Everyone who meets him is quite taken aback by how grown up he is. ” - dup 5q35.3, 8 years

“ She is lovely, bright, chatty, cheeky, full of energy, very determined and can be stubborn! She can be anxious but likes to be independent. She is a very happy, healthy, active girl who is very tiny. She is very nice-natured and well-liked by others and is very sociable. She is also very nurturing in nature and would like to be a nurse (like me!) when she grows up. Anything to do with art and craft she loves, also music, dancing and any messy play or water play. She does after school activities (gymnastics, swimming, karate). ” - dup 5q35.2q35.3, 6 years

“ She is sweet-natured, bubbly, smiley, kind-hearted and affectionate. She has a great imagination and loves singing and stories, and playing with 'babies'. She can lack confidence in crowds, doesn't like noise, and can be immature for her age. ” - dup 5q35.2q35.3, 4 years

“ He has a very happy personality and is very loving and caring. He can be quite quiet when he's in strange surroundings and at times frustration (regarding communication or hunger) can cause him to become angry. He can lash out at others during this time, but generally is quick to calm down. He likes playing music on toy instruments and dancing, and loves being outdoors and watching the vehicles on the road. He loves swimming, the beach, and has recently learnt how to scoot on his scooter. ” - dup 5q35.2q35.3, 4 years

“ She is a generally happy and placid child. She does have violent meltdowns but these are few now. She likes watching movies and is trying to learn new songs to sing. ” - dup 5q35.3, 9 years

“ He is generally happy, loves being helpful, and is very kind. He needs constant adult contact and is especially close to me. He also has a good sense of humour and responds well to rules when in the mood, but he can also be quite challenging and a little naughty, which can happen very suddenly. He goes very hyper at times and this is when he becomes hard to handle or get to sleep. ” - dup 5q35.2q35.3, 9 years

“ She is very bubbly, happy, funny and sociable, but has some meltdowns. She loves messy play, dancing and singing. ” - mosaic dup 5q35.2q35.3, 5 years

alphabet. He uses a lot of long phrases - repeated and sometimes inappropriate in context - with monologues about his narrow interests. His receptive language is slightly better than his expressive language.” - dup 5q35.3, 10 years

“ He started to speak at around three years of age. He will often speak in short sentences/phrases. One of his recent longest sentences was: “What’s the man on the roof doing?”. He knows hundreds of single words but wouldn’t put complex sentences together yet. We learnt Lamh (a manual sign system from Ireland) when we weren’t sure if he would communicate verbally. It helped us in the initial stages of speech as it would help us understand his words better. We believe that he can understand a lot more than he can express.” - dup 5q35.2q35.3, 4 years

“ He speaks quite well; I’m not sure if this is because I am a chatter box! Typical sentences are: “I worked on the farm today.”. He talks like a baby when stressed or ill, and he can do this randomly.” - dup 5q35.2q35.3, 9 years

“ My son uses a wide range of vocabulary, including words that an adult would typically use.” - dup 5q35.3, 8 years

Personality

Every child is an individual and not all personality traits will be related to the chromosome disorder. Parents frequently told us about loving, happy, caring, friendly, kind and determined children who particularly enjoyed sensory activities involving music, singing and dance. Many participated in a range of sporting and outdoor activities, from swimming to karate.

Some also told us that their child could experience sudden mood changes and “meltdowns”, leading to challenging behaviours. Many were anxious or shy in crowds, new surroundings or with strangers (see “Challenging behaviours”).

“ She is happy, reflective and has a strong will and opinions. She is a very caring person and puts the needs of others first, to make them happy. She also does this when playing with younger children but is very subtle about it so that it is often not recognised. She tends to pick out people she wants to be with very carefully. She enjoys reading, drawing, swimming, and now, at age 13, computer games.” - dup 5q35.2q35.3, 13 years

“ She is very shy at first, but once comfortable is very loving and friendly. She likes to watch and play with other children. She is very protective of her



Appearance

Consistent, shared facial features do not appear to have been identified in children with 5q35 duplications.

Some children may have subtle facial features that are not obvious to a parent but can be identified by a paediatrician or clinical geneticist, since professionals looking after children with genetic changes are trained to notice physical features that may suggest a child’s difficulties are of a genetic origin. Where facial features were noted, the most common were: a thin upper lip; a broad nasal bridge; a small mouth; low-set/unusual ears; skin folds at the inner corner of the eye; and widely-spaced eyes.

An unusually small head (microcephaly) was common among children with a duplication including the *NSD1* gene (5/9 *Unique* survey; 25/31 medical literature). The jaw may also be unusually small (micrognathia), including in some children in the medical literature (5/30) and one *Unique* child.

One boy with a 5q35.3 duplication had an unusually large head (macrocephaly). It appears that a girl with a 5q35.3 duplication had a head that could be considered larger than is typical, while her brother’s skull was flattened on one side (plagiocephaly) (Dikow 2013; Novara 2014; *Unique*).

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

Many babies and children were late to achieve their ‘milestones’ of sitting and walking, although the delay was often mild.

These included 9/12 members in the *Unique* survey, 9 further members in the *Unique* database (DB), 20/31 cases in the medical literature and 11 cases in DECIPHER. There is a wide range of eventual ability, with some children acquiring mobility skills around the same age as typical children and others showing more obvious delay.

Among *Unique* children, rolling over was achieved between three and 9 months; sitting between 8 and 11 months; crawling or bottom shuffling between seven and 18 months; and walking independently between 12 months and three years (with most walking by two years).

Mobility may be affected by abnormal muscle tone: roughly half of *Unique* children had either low tone (hypotonia), high tone (hypertonia) or a combination of the two. Babies with low muscle tone at birth feel floppy to hold and have obvious head lag. Low muscle tone generally improves with maturity but may still be present in adults. Regular physiotherapy (PT) helps, and the use of orthotics such as support boots may also help increase mobility.

Parents told us that their children enjoyed a range of physical activities but seemed to particularly enjoy swimming, dancing and outdoor activities (Dikow 2013; Novara 2014; Reis 2017; Unique).

“ PT was required to help her walk but she no longer has it. Loves to swim and play outdoors. ” - dup 5q35.1q35.3, 5 years

“ He has received PT since he was 22 months. He was quite floppy when he was a baby and had low muscle tone in his face and body. When he is excited, he tenses his body (arms especially). He doesn't see the physio very often anymore as he is developing gross motor skills quite well himself. He likes playing music on toy instruments and dancing. He loves being outdoors, watching the vehicles on the road, swimming, the beach, and has recently learnt how to scoot on his scooter. ” - dup 5q35.1q35.3, 4 years

“ He loves the outdoors but can get cold quickly if not busy. Loves riding his bike or scooter and likes gardening/nature trails. He does not have a good attention span so he has a lot to do in the garden e.g. trampolining, throwing a ball to the dog, football or other ball games. ” - dup 5q35.2q35.3, 9 years

“ Needs help with walking, steps, jumping and has hypotonia (especially in legs and arms). ” - dup 5q35.3, 9 years

“ Learning to ride a bicycle and swim has taken ages. We think she was scared instead of unable. Since she had to change bikes, due to growing out of the smaller one, she doesn't feel confident any more. ” - dup 5q35.2q35.3, 13 years

“ PT to help develop core strength as difficulty with balance and fine/gross motor skills. She loves music and dancing, any messy play or water play, and does afterschool activities e.g. gymnastics, swimming, karate. ” - dup 5q35.2q35.3, 6 years



There are many reasons why speech may be delayed, 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, children typically used long, complex sentences. A few children occasionally found it difficult to make clearly intelligible speech sounds, which can make communication with strangers a challenge. Many parents believed that their child could understand a lot more than they could express.

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. Any concerns around hearing should also be acted on early.

“ She loves to talk! At 20 months, her comprehension and understanding were good and her speech was well developed. At six years, she talks in full sentences, but has difficulty repeating things back on the spot. ” - dup 5q35.2q35.3, 6 years

“ She has a speech delay and has received speech therapy since she was three-and-a-half years old before starting pre-kindergarten, which continued once she was enrolled in school. This benefitted her greatly; she began saying words and sentences very quickly. Now, she mainly uses short sentences e.g. “Mama, I want to go to the park.”. I believe she can understand more than she can express. ” - dup 5q35.1q35.3, 5 years

“ She started speaking at 10 months. At 7.5 years she is bilingual and speaks in long, complex sentences. ” - dup 5q35.2q35.3, 13 years

“ By 18 months, she had started talking, had 10 spoken words and babbled a lot. She sometimes finds it hard to make sounds clearly and her receptive language is better than her expressive language. She uses sentences like: “Mummy, can we make a cake today?”. ” - dup 5q35.2q35.3, 4 years

“ His speech was severely delayed, with only single words at three-and-a-half years. He could speak in phrases by five years but had echolalia (repetitive speech patterns). By 8 years, he had started constructing his own sentences, but still struggled with pronunciation and grammar. When speaking he has trouble distinguishing between different letters of the

to have a weakness: her hearing is normal, but she has trouble hearing, retaining and understanding information when other voices are around, so the classroom is a challenging environment. Handwriting is difficult for her, she still gets d and b mixed up. She can draw, but poorly for her age - she is six but draws more like a four-year-old. She can read if she's in the mood! Using a programme like "Reading Eggs" has been really helpful. She works well in a 1:1 situation, but needs extra explanations to be repeated and it is best to only give her one to two tasks at a time. I paid for all the assessments to be carried out privately (auditory processing disorder, occupational therapist, educational psychologist); had I gone via the public or free system none of this would have happened as she isn't behind at school or deemed to need testing - yet. This is why I had them done in the first place, to get help in place now. She has a 1:1 teaching assistant for 40 minutes, four times a week." - dup 5q35.2q35.3, 6 years, New Zealand

" She achieved her milestones at the expected times. She is very good at reading and writing for her age, but is not very competent in maths. She is in mainstream schooling." - dup 5q35.2q35.3, 9 years, New Zealand

" She is severely intellectually disabled and attended regular kindergarten with support and a special early intervention program. She now attends a special school for her primary education." - dup 5q35.3, 9 years, Australia

" He was tested at seven years and re-tested at 11 years and was found to have mild learning difficulties (IQ 74-77). He still can't read, write or remember numbers. His drawing is affected by his being a little bit behind with finger grips. He learns within narrow interests and repeated kindergarten as he wasn't ready for school. He attended a state primary school from Prep (Reception) to Year 2. He is now home-schooled. He still can't read or write, but is happily learning in his own way." - dup 5q35.3, 10 years, Australia

Speech and Communication

A "typically"-developing baby usually coos and babbles by six months, produces speech-like noises in the next few months and says their first understandable words around their first birthday. While roughly half of *Unique* children with a 5q35 duplication including the *NSD1* gene (5/9 survey; five cases DB) had speech and language that was completely fluent and/or age-appropriate, others (4/9 survey) experienced speech delay.

Of those *Unique* children with a 5q35.3 duplication, one had no speech delay, while for two siblings with the same duplication, one had severe speech delay and one was non-verbal.

There are also documented cases of individuals with speech delay in the medical literature (Dikow 2013; Rosenfeld 2013; Novara 2014; Reis 2017; DECIPHER; Unique).



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

A delay in the development of hand use and hand-eye coordination was observed in most children.

These skills are essential for tasks such as holding a bottle, using cutlery, playing with toys, holding a pencil and fastening clothes. Some parents suggested that hypermobile joints in the fingers and thumbs, hypotonia and/or hypermobile joints contributed to difficulties.

Special chunky cutlery, cups with handles and having food cut up have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard can often be easier. 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 continue to need help with dressing and undressing for longer than expected and difficulties with fastenings may persist. They may also require assistance in tasks such as brushing teeth and washing. Toilet training was usually delayed, with the experiences of *Unique* families suggesting that although a minority of children achieve bladder and bowel control at or around the usual age, many take longer (Unique).

" She manages most things well, but due to hypermobile finger joints, fine motor skills are a challenge. She can write, use a fork etc., although handwriting is difficult for her, and she can draw, but poorly for her age. Toilet training was horrible - she was always "too busy" to go. Finally achieved during the day at around three-and-a-half years, but at night she is still very wet." - dup 5q35.2q35.3, 6 years

" She can't use a knife yet, but she gets dressed - although not in suitable clothes. She can't manage a bra, buttons etc. that involve fine motor skills." - dup 5q35.2q35.3, 16 years

" She has achieved her fine motor skills milestones such as writing and drawing, but they were delayed. She can't cut with a knife and her handwriting is poor. She can get dressed, but not appropriately for the weather." - dup 5q35.3, 9 years

" She achieved her fine motor skills developmental milestones at the expected times. She is very good at reading and writing for her age. She was urinary continent at around two-and-a-half years, with faecal continence at around six years." - dup 5q35.2q35.3, 9 years

" Her fine motor skills are getting better, but they were delayed. She started

drawing simple things at four years, but doesn't draw many pictures. She has started to read now at nearly six years and is writing well. She was toilet trained by almost four years and is dry at night, but sometimes she still wets in the daytime when busy.” - dup 5q35.2q35.3, 5 years

“ Fine motor skills are not very good. She had issues holding a pencil and cutlery - she preferred eating with her hands anyway. Had OT once a week from four-and-a-half years, after the physiotherapist suspected sensory integration disorder, which helped a lot. After an assessment at 8 years we have gone once a year until age 11. Now, I call her just to report how it's going. OT helped a lot with sensory integration: she suffered so badly from motion sickness that we didn't have a car. Since age 11, we have a car! ” - dup 5q35.2q35.3, 12 years

Ability to learn

The range of learning ability is very broad, but children with a 5q35 duplication often need support with their learning.

Some children with more mild learning difficulties (LD) attend mainstream schools and are able to follow the standard curriculum, where necessary benefitting from a dedicated support worker for specific areas of concern; others have been assessed as having more severe intellectual disability (ID) and require considerable support.



The *Unique* survey revealed that 8/9 children with a 5q35 duplication including the *NSD1* gene had LD or ID, most often mild to moderate (four mild; two moderate and one severe).

Of those children with a 5q35.3 duplication, all three had LD or ID (two mild; one severe), including two siblings with the same duplication. One sibling was more mildly affected, while the other sibling was more severely affected (*Unique*).

A similar pattern is seen in the medical literature, with roughly two-thirds (23/30) of children and adults having a confirmed diagnosis of some degree of LD/ID, ranging from mild to severe. Those individuals without apparent difficulties included a 9.5-year-old boy with a 5q35.2qter duplication and a small boy of almost three years with a 5q35.2q35.3 duplication including *NSD1* (Dikow 2013; Jamsheer 2013; Novara 2014).

Many *Unique* children attended a mainstream school, often with 1:1 help in the classroom or other provisions. A few children transferred to a special educational needs setting at a later stage, where this was felt to be beneficial; others attended a special educational needs school throughout their education. One child was home-schooled.

Where you have concerns, early intervention is important - 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. *Unique* has a dedicated guide to “Education” in the practical guides for families section of our website.

“ He has moderate learning disability and dyslexia. He has been unable to access the curriculum since starting primary school, and was not retaining information or progressing. He has been working with a Statement since Year 4. At 11 years, he is in mainstream secondary school and is making very slow progress. However, since starting Year 7 his progress has been more rapid than in primary. He is unable to read freely or write, has no concept of phonics and really struggles with maths. He receives an enormous amount of support in school from a TA and SENCO, which he is extremely reliant on. During his Year 4 we did explore the possibility of him attending a moderate learning difficulty school; however, his application was rejected by the county on two occasions as his overall profile did not meet the criteria and, upon visiting the school, myself and my husband agreed with this. ” - dup 5q35.2q35.3, UK

“ At six years, she is in mainstream education with help and is approximately one and a half years behind. She can read and write and started drawing simple things at four years, but doesn't draw many pictures. Her strengths are phonics and writing. She doesn't have an EHC plan, but is having special help at school and is slowing getting there. ” - mosaic dup 5q35.2q35.3, 5 years, UK

“ From age three to four years, she attended a public (state) nursery in the Netherlands. From four years until now, she is in a public (mainstream state) primary school. She is one year behind in maths and is working with a remedial teacher for one and a half hours, once a week, in a one-to-one setting. She is bilingual in Dutch and German, and is learning English without a problem; she is very interested in languages in general. We have to decide on a secondary school within the current school year so we are also thinking about special education, because of her problems in maths. In general, her learning abilities have improved with age and we are sure that the problem with maths will also be solved at some time. ” - dup 5q35.2q35.3, 13 years, Europe

“ Nothing diagnosed yet, as they don't diagnose with a specific learning difficulty until age 8. She has been tested for auditory processing disorder, but again they don't diagnose until age seven, although she has been shown