Unique

Understanding Chromosome & Gene Disorders

# 15q11.2 Microduplications

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# 15q11.2 microduplications

A 15q11.2 microduplication is a rare genetic condition caused by the duplication of a small piece of genetic material from one of the body's 46 chromosomes – chromosome 15.

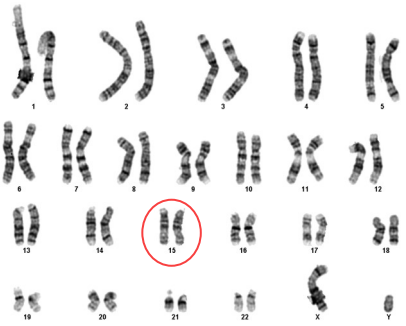
For typical development, chromosomes should contain the expected amount of genetic material (DNA). Like many other chromosome disorders, having an extra piece of chromosome 15 may affect a child's health, development and intellectual abilities. The symptoms observed in people with a 15q11.2 microduplication are variable and depend on a number of factors including what and how much DNA is duplicated.

## Background on chromosomes

Our bodies are made up of different types of cells, almost all of which contain the same chromosomes. Each chromosome consists of DNA that codes for our genes. Genes can be thought of as individual instruction booklets that contain all the genetic information that tells the body how to develop, grow and function.

Chromosomes come in pairs with one member of each chromosome pair being inherited from each parent. Most cells of the human body have a total of 46 chromosomes (23 pairs). Eggs and sperm, however, have 23 unpaired chromosomes, so that when they join together at conception, the chromosomes pair up to make a total of 46.

Chromosome pairs are numbered 1 to 22 and the 23rd pair comprises the sex chromosomes that determine biological sex. Males usually have one X chromosome and one Y chromosome (XY), and females usually have two X chromosomes (XX).



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

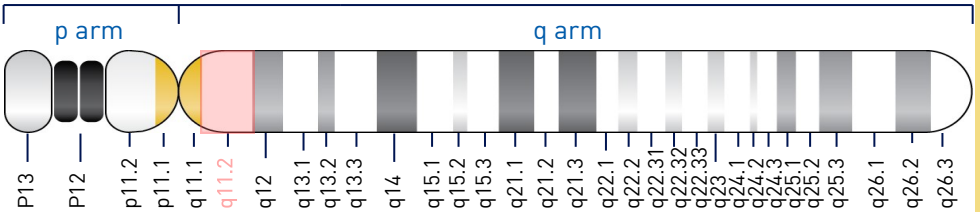
## Sources

The information in this booklet is drawn from published medical literature, databases and *Unique* members. The first-named author and publication date from articles 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. 20 families completed a *Unique* survey in 2018.

## Looking at 15q11.2

Chromosomes can't be seen with the naked eye but if cells are prepared in a specific way, the chromosomes can be stained and viewed under a microscope to show a distinctive pattern of light and dark bands. You can see the banding pattern for each chromosome in the image on page 2, and a more detailed diagrammatical view for chromosome 15 in the image below.

### Chromosome 15

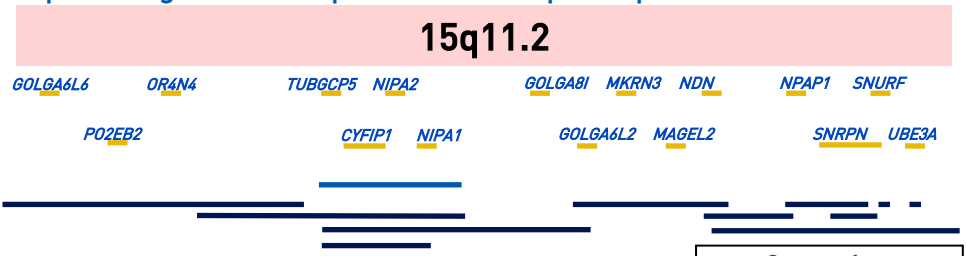



Each chromosome has a short (p) arm and a long (q) arm. Bands are numbered outwards starting from where the short and long arms meet, at a point called the centromere (coloured yellow in the image above). Region q11.2 is close to the centromere on the long arm (q) of chromosome 15 (shaded pink in the image above).

### Duplications in region 15q11.2

The duplications discussed in this information guide are commonly referred to as 15q11.2 microduplications. There are regions in this part of chromosome 15 where breakage and duplication are more likely to occur (due to repetitive pieces of DNA), so some people will have very similar duplications. Others will have a slightly larger or smaller duplication, or a different duplication in the same chromosomal band that contains different genes (as shown in the image below). Families who receive a slightly different genetic test result, such as a larger 15q11.2q12 duplication may find our 15q11q13 duplication guide more appropriate since a duplication that includes DNA from the chromosomal band 15q12 includes a number of other significant genes.

### Important genes in 15q11.2 and example duplications




A common 15q11.2 microduplication includes the genes *TUBGCP5*, *CYFIP1*, *NIPA2* and *NIPA1*. This region is often referred to as the Burnside-Butler region (shown as a blue line above).

In the past, chromosomal duplications were routinely identified by the basic band staining procedure shown on page 2 (known as a karyotype) but most microduplications are too small to be seen using this technique. A laboratory technique called FISH (fluorescence *in situ* hybridisation) was later developed, in the 1990's, which enabled sections of chromosomes to be analysed in more detail. This technique uses fluorescently labelled pieces of DNA that match the DNA in specific places on a chromosome so is only offered as a test if there is a suspected change in a specific region of a chromosome. More recent tests are now routinely available that allow DNA to be analysed in greater detail such as microarray comparative genomic hybridisation (array CGH) and SNP (Single Nucleotide Polymorphism) microarrays. Array tests can detect very small duplications even when a specific diagnosis is not suspected. For 15q11.2 microduplications, the duplicated piece of genetic material is commonly presumed to be placed on chromosome 15 next to the original piece of DNA, however arrays cannot identify the location of the duplicated DNA.

## Chromosome test results

Your clinical geneticist or genetic counsellor will have given you detailed information about the piece of DNA that has been duplicated in your child (and perhaps also yourself and/or other family members). The information you are given will include any significant genetic changes that are identified and which significant genes are included in the changes. This will most likely include an array CGH test result such as that detailed below.

## Array CGH example:

### arr[hg19] 15q11.2 (22728371-23260335)x3 dn

arr The analysis used microarray technology

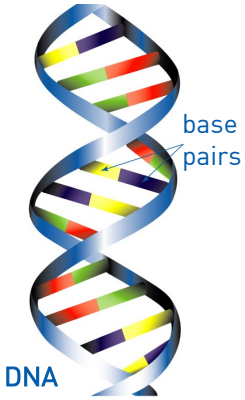
hg19 This is the reference DNA sequence that the base pair numbers refer to, in this case human genome build 19 (for more information, see page 5)

15q11.2 The analysis revealed a DNA anomaly on chromosome 15, region q11.2

(22728371-23260335) The DNA anomaly is identified by its base pair numbers (the points where the chromosomal change has occurred). In this example, the DNA anomaly lies between base pairs (bp) 22728371 and 23260335. This region covers 531,964 base pairs, or more simply ≈0.5 Mb (1 Mb = 1,000,000 base pairs)

x3 There are three copies of the piece of DNA specified. Since there should be 2 copies of chromosome 15, this shows that the DNA anomaly is a duplication

dn The duplication occurred *de novo* (as a 'new event'). The parents' chromosomes have been checked and no duplication has been found in this region of chromosome 15



If a duplication is identified as *de novo*, it is very unlikely to have been inherited. If a test result is followed by mat, the duplication has been inherited from the mother (maternal); if it is followed by pat, the duplication has been inherited from the father (paternal).

If a duplication is found to be inherited, other family members may be offered a DNA test such as a microarray, FISH or qPCR (quantitative Polymerase Chain Reaction; a quick test that can be designed specifically for the duplicated piece of DNA to identify any increase in copy number). A FISH test (see page 3) can also confirm if the extra piece of genetic material has been placed on chromosome 15 next to the original piece, and can help indicate somatic mosaicism. Somatic mosaicism is when not all cells in the body contain the extra piece of genetic material. In such rare cases, the outcome of having a duplication may depend on which cells in the body contain the extra DNA.

You may wish to compare your child's results with others who have the same or a similar duplication to help understand your child's development. While this may help identify common symptoms, it is important to remember that the same duplication can have very different effects on different people, or no apparent effect at all. Siblings with the same parents and the same duplication can have very 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.

## 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 therefore the duplication coordinates 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 in this guide is based on the Genome Reference Consortium (GRC) human (h) genome assembly number 37 (GRCh37), which was released in 2009. You will often see the DNA sequence data for this assembly referred to as hg19 (human genome 19) on a genetic report.

The databases commonly used by clinical geneticists and Unique will soon move to a more recent assembly named GRCh38/hg38, which was released in 2014. Genetic reports will at some point also be altered, so genes and genetic changes may have new base pair numbers.

## How common are 15q11.2 microduplications?

As shown on the bottom of page 3, there are a number of different possible microduplications within 15q11.2, some of which are more common than others. Some are thought to be benign, meaning no symptoms would be expected; some are thought to be pathogenic, meaning symptoms would be expected (e.g. those that disrupt the *UBE3A* gene); some are of uncertain significance.

**Duplication of the Burnside-Butler region**: The most commonly identified microduplication located within 15q11.2 is known as the Burnside-Butler region (named after the researchers who first reported symptoms in people with a deletion of the same region). These duplications can vary in size slightly but all contain the *TUBGCP5*, *CYFIP1*, *NIPA2* and *NIPA1* genes.

Recent research has shown that 15q11.2 Burnside-Butler duplications were identified in 0.42% of people referred for genetic testing (215 out of 51,462 people (Mohan 2018)), a similar value to that observed in earlier research (77 out of roughly 17,00 people, Burnside 2011). However, the symptoms observed vary greatly and a significant number of apparently unaffected people with this duplication, known as healthy carriers, have also been identified (20139 out of 420247 people (0.48%) Kendall 2019). The majority of children with this duplication reported in the medical literature have inherited the extra piece of DNA from an apparently unaffected, or mildly affected parent. The identification of such a significant number of people apparently unaffected by their Burnside-Butler region duplication has made it difficult for geneticists to assess whether this duplication is the cause of difficulties experienced in children and adults.

The association of this particular duplication with the symptoms observed is therefore currently being reviewed (2019). Whereas this duplication was initially described as the cause of neurodevelopmental difficulties observed in many children and adults, it was later explained as a genetic change that could present a susceptibility to neurodevelopmental difficulties.

A duplication of the Burnside-Butler region could be described as having 'reduced or incomplete penetrance' meaning not everyone who has the duplication will have an outcome and 'variable expressivity' which means the symptoms can be different for people with the same duplication. The reasons for this are unknown but could include different activity levels of duplicated genes in different people (Picinelli 2016), a possible parent of origin effect (POE, Davis 2019) and the possibility of other unidentified genetic alterations in a person's genome (their complete set of genes).

Due to the number of apparently unaffected individuals, many laboratories in the UK are no longer reporting this genetic change if identified during genetic testing. This now leaves families, who have been given this diagnosis as an explanation for their child's difficulties, in a confusing situation. Families who have been given this diagnosis, and no other identified genetic change, may wish to contact their genetic service centre to ask if further testing is possible to help provide an alternative or additional explanation for their child's difficulties.

## Unique members

Unique currently (2019) has 70 members with a 15q11.2 microduplication who live world wide, 16 members also have changes to other chromosomes or additional changes on chromosome 15. Only those with a 15q11.2 microduplication (and no other chromosomal anomaly) are considered in this guide since, for others, the reason for some of their clinical features may be due to additional chromosomal alterations. This guide may however be of use to such families to partly explain their child's difficulties.

Twenty families completed a Unique survey in 2018. Survey responses were received for 16 boys and four girls, all of whom (bar one, who was unable to provide a detailed genetic test result) had a duplication in the Burnside-Butler region (including the *TUBGCP5*, *CYFIP1*, *NIPA2* and *NIPA1* genes). The majority of information in this guide will therefore be related to duplications of the Burnside-Butler region. If your family's duplication does not include this region, some of the following information may still be of use but please refer to pages 22 and 23 for more specific details regarding different duplications within region 15q11.2.

## Why did this happen?

When sperm and egg cells join they form a single cell and this cell must continuously make copies of itself (and all its genetic material) in order to produce the billions of cells that are necessary for human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated replication process, parts of a chromosome are lost, duplicated and/or become rearranged. The reason the duplication occurred in this specific region of chromosome 15 is thought to be due to the repetitive nature of the DNA sequence in this region. It is important to know that as a parent there is nothing you could have done to prevent this from happening. No environmental, dietary or lifestyle factors are known to cause 15q11.2 microduplications. There is nothing that either parent did before, during or after pregnancy that caused the duplication.

## Can it happen again?

If a parent is found to have the same duplication as their child, the possibility of having another child with this duplication is 50% in each pregnancy. If neither parent is found to have this chromosomal change, it is unlikely that they will have another child with a 15q11.2 microduplication. Very rarely, parents are identified as having unaffected chromosomes by a blood test, but a few of their egg or sperm cells carry a chromosomal change. Geneticists call this germline mosaicism and it means that such parents can have more than one child with the same chromosome disorder. If they wish, parents can discuss their specific recurrence risks with a genetic counsellor.

If your child with a 15q11.2 microduplication goes on to have children of their own, the chances of passing on the duplication to their child is 50%. Your child's ability to look after their own child is very likely to be closely related to their own learning ability and behaviour.

## Possible features

Symptoms associated with 15q11.2 duplications vary greatly, some symptoms appear to be more common than others. The following is a list of features that have been observed in people affected by their 15q11.2 microduplication:

- Learning difficulties
- Speech and language difficulties and delays or absent speech
- Autism spectrum disorder (ASD) or other behavioural difficulties
- Seizures
- Developmental delay
- Sensory processing disorder
- Anxiety and/or emotional lability (rapid change in type/strength of emotion)
- Hypotonia (low muscle tone)

It is important to note that each person will have different developmental and medical concerns. A significant number of people with a 15q11.2 duplication have none of the features mentioned in this information guide, while a few have many. Symptoms will also depend on the size and content of the duplication, possibly the chromosome of origin, as well as the unique genetic makeup of each person. Other less common features have also been reported in association with 15q11.2 microduplications and are discussed later in this information guide.

## Pregnancy and birth

Most 15q11.2 microduplication pregnancies are reported as uncomplicated and babies are born at or near their due date. Eight Unique members mentioned concerns during pregnancy but each concern was different and can occur during pregnancies of babies without chromosomal duplications. Unique members mentioned gestational diabetes, high blood pressure, an excess of amniotic fluid, reduced movement of the baby and a kidney anomaly identified during a routine ultrasound. One family mentioned their child was born premature.

## Newborn

Most babies with a 15q11.2 microduplication are born with a birth weight within the normal range. Eight Unique families informed us that their babies experienced some difficulties during the new-born period, mainly feeding difficulties.

Half of the families who completed the Unique survey described their baby with a 15q11.2 microduplication as being 'floppy' in the newborn period. Health professionals call this hypotonia and it can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Hypotonia can also result in delays reaching developmental milestones such as rolling, sitting, crawling and walking.

## First signs

Since symptoms observed in people with a 15q11.2 microduplication are so variable, babies and children are diagnosed at various stages of development. Babies with a 15q11.2 microduplication are not commonly reported as having physical problems such as hernias (although four Unique members have mentioned their baby had a hernia), or strong facial features that have been associated with other genetic changes. The majority of Unique members reported that their child was offered a genetic test due to concerns such as developmental delay, delayed speech, hypotonia or delayed motor skills. Others have been identified due to behavioural diagnoses such as ASD (autism spectrum disorder) or ADHD (attention deficit hyperactivity disorder). Some were offered a genetic test due to seizures.

## Appearance

Children with a 15q11.2 microduplication may have subtle facial features that are not obvious to a parent but can be identified by a paediatrician or clinical geneticist. Facial features can be very subtle and children may not look very different to other children and may closely resemble their siblings and/or parents. 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. Making a note of these may help establish common features observed in children with the same genetic change and therefore aid diagnosis. Shared facial features do not appear to have been identified in children with 15q11.2 microduplications.

## Feeding and growth

Half of the families who have provided information about feeding have mentioned that their child with a 15q11.2 microduplication had feeding problems as a baby. This can be due to a number of reasons. Babies with hypotonia (low muscle tone) may find breast feeding or bottle feeding very tiring. They may take a long time to feed or need to be fed more often. If a baby's nutritional needs cannot be met, they may require supplementation with a high energy formula or via a nasogastric tube (a tube leading to the stomach that is inserted via the nose to allow all feeds and medicines to be taken directly).

Some babies have reflux, where feeds return up the food pipe from the stomach. If necessary, this can be controlled with medication and feed thickeners as well as careful positioning. 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. A few Unique families mentioned milk leaking out of their babies mouth while they fed. Feeding may also be affected by constipation.

❝ We suspected he was tongue tied as he was unable to consume his feeds without the majority spilling out the sides of his mouth. ❞ - Age 5

❝ Right away he wouldn't eat. We tried nursing, bottles, I had lactation consults,

doctors appointments etc. and no one knew what to do. Finally at 4 months he was referred to a feeding clinic where he was diagnosed with failure to thrive and dysphasia. ” - Age 18

Families mentioned that as their child grew they developed a healthy appetite and some observed a tendency for their child to overeat. Recent research has identified a slight but statistically significant increase in Body mass index (BMI; Kendall 2019), in people with 15q11.2 duplications of the Burnside-Butler region.

“ When he was a baby he had to be tube fed. He was always very particular about food not being separated (i.e. a hamburger falling out of is bun is "broken" or a hotdog being cut up), as an adult he eats anything that is placed on a plate. He tends to eat quickly though and needs to be reminded to slow down, he had to be resuscitated as a child from choking. ” - Age 28

“ We have to monitor intake, he doesn't feel full. Will eat until sick. ” - Age 18

## Sleep

About a quarter of the families who gave us information about their child's sleeping habits remarked that their child has (or has had) some form of regular sleep disruption. Families informed us that their children find it difficult to 'switch off' and fall asleep at night, some children do not sleep for long periods of time and wake repeatedly in the night, some wake far too early in the morning.

The reasons for sleeping difficulties in children with chromosome disorders are not yet well understood and may be different for each child. One family mentioned their child was diagnosed with a sleep disorder and four families mentioned the intermittent and temporary use of melatonin (a hormone naturally produced by the body in response to day/night cycles that can help synchronise a child's body clock). Seven families informed us that their child (including adult children) have or had sleep apnoea (pauses in breathing or shallow breathing during sleep). One family mentioned their child was diagnosed with restless leg syndrome, and another mentioned their child suffers from leg cramps during the night. Half of the families who completed our survey did not mention their child had any form of sleep problem.

“ He goes to bed every night at 9pm but will come down stairs multiple times. He usually falls asleep between 10-11 and is up anything from 3-8 times a night. When he's up he will reorganise his bedside table, doodle, read, get out of bed for a fidget toy. He always says 'I just can sleep'. Before bed we try salts (magnesium sulfate) in the bath, low lights, oils. He takes a hot water bottle to bed and a teddy. We have tried visuals but he wasn't keen on them. He does the same routine every night even weekends. Awaiting sleep specialist. ” - Age 10

“ Huge problems with sleep. Extremely difficult for the first 5 years when she was up most of night. She still tends to wake between 2-4am in the morning. Can also take a long time for her to settle at night. Varies from day to day.

However, going to school has made her more physically tired which has been a positive change. ” - Age 8

“ Until recently has was waking up every couple of hours. We've been giving him melatonin at night-time which seems to be starting to get him into a better cycle. ” - Age 2

## Child development

Once your child has shown their individual pattern of development it will become easier to predict their abilities and possible longer term difficulties. Unique members have reported a wide range of difficulties in their children with a 15q11.2 duplication. Developmental delay (when developmental milestones are not reached within an expected time range) was mentioned by all families who shared this information about their child.

## Gross motor skills and mobility

Roughly half of the families for whom we have information regarding motor skills mentioned that their child's gross motor skills are affected, many mentioned their child started to walk late. For some, this may be related to hypotonia and/or joint hypermobility. Four Unique families mentioned their child had hypertonia (increased muscle tone) either in the arms and legs or legs alone.

“ He only sat at 18 months. Walking at 2 after significant private physio. He is still very wobbly, and walks with his feet pointed inwards and on his toes. ” - Age 2

“ One leg was weaker. Didn't walk until around 2. She leant forward as she walked which made her unsteady. I think she might have hypermobility in one knee. Mobility and strength have increased with age. She is actually very athletic and has very good core strength but her inability to follow instructions in a group setting makes sport difficult. ” - Age 8

“ He has always been floppy and uncoordinated. He falls often, has an awkward gait. Low muscle tone and diagnosed with Chorea. Muscle pain as he gets older. Struggles to do things like skip or jump. ” - Age 18

## Fine motor skills

Half of the families who provided information regarding fine motor skills mentioned their child with a 15q11.2 duplication had difficulties with fine motor skills ranging from mild to severe. Most parents mentioned poor hand use and coordination and delays in meeting milestones.

“ He currently uses different types of pencils to help with his finger control and stability. ” - Age 10

“ He cannot show finger numbers like 3 or 6. Can't snap fingers. Can't tie shoes. Struggles with all finger & hand movements. ” - Age 10

❝ Fine motor skills are still a problem. Although there is an improvement with age she still struggles with her dexterity and has little interest in tasks involving focused use of the hands as she finds them challenging. ❞ - Age 8

❝ He is now 18 and still needs help with buttons, snaps, zippers, bathing , trimming nails. ❞ - Age 18

## Self Care

Families have informed us that self care is commonly delayed but eventually achieved. Toilet training is commonly delayed, perhaps more so at night.

❝ She still remains in pads. She has learned to use a toilet but not consistently enough to come out of pads. This is in part down to not communicating that she needs the toilet effectively enough when outside the home. She is still unable to wash/get dressed alone or clean her teeth. ❞ - Age 8

❝ He needs to be supervised during teeth cleaning and personal self care. He can use the toilet himself but won't always go and will hold it in, or if it's a bad day I will need to remind him to go to the toilet. He still can't do laces so wears strap boots/shoes. He can dress himself but will dress messily. I've to set out his clothes in the correct order to be put on. He always puts thing on back to front. ❞ - Age 10

❝ Didn't potty train until age 5. Still cant wash or dry body on his own. Struggles dressing. ❞ - Age 10

❝ He was dry from nappies in the day at 3/4 years and night time shortly after. He does have accidents in the day time though. He can get dressed by him self and can manage to get dressed in most things that don't have buttons or zips. He cannot tie his laces. He can clean his teeth but needs adult supervision. He loves water and bath time. ❞ - Age 5

## Ability to learn

Most children who appear to be affected by their 15q11.2 microduplication described in the literature, and members of Unique, experience learning difficulties and for some this may be compounded by hearing and/or vision problems. While some children are identified as having a mild learning difficulty, the learning abilities of others are more severely affected. Some children attend a mainstream school and some have a dedicated support worker, others attend a school specifically for children with special educational needs. If your child is diagnosed early enough they may benefit from early intervention programmes. Children may also benefit from speech and occupational therapy sessions.

❝ Since our family has been at the same school for years now, our school has been very willing to work with us to make a comfortable, loving environment for her. She attends all of her therapy out of school, so school is for social growth and so she can be around typical peers. ❞ - Age 4

❝ He is in mainstream school. I have been fighting since he was in P2 for more help with him. He is in P5 and at a learning level of P3/4, he sees the Additional Support for Learning teacher once a week. He has a wedge cushion to sit on in class, he needs movement breaks. ❞ - Age 10

❝ He attends a state maintained special needs school for children with severe learning difficulties and ASD. He is in a classroom with 5 other children with 4 members of staff. He is very well supported at school. ❞ - Age 5

❝ In public school, contained classroom. Receives Physical, occupational and speech therapies. ❞ - Age 8

❝ She attends a special school. She made the move at 4 and went into reception. Although we still have huge challenges I noticed immediately when she went to a special school that she was much happier. Having small classes meant a less noisy and overwhelming environment. From our perspective we also became less stressed as instead of being told what she couldn't do the focus become on what she could do. A much more positive environment. My advice is try to get your paper work sorted and make the change as soon as is practical. ❞ - Age 8

❝ I home school him. This allows him to keep working on skills until he masters them. It also helps to rebuild skills after loss from seizures. It allows for more individual therapy sessions. He can take breaks as needed. Bad days can be adjusted to meet his individual needs. ❞ - Age 10

❝ He did not start school until he was almost 7. He didn't meet any of the requirements so it was best to keep him home. Once he began school he was always behind educationally. He repeated grade 6 to give him some time to catch up. He was on an IPP (Individual Pupil Program). He did stay an extra year in Grade 12 as well and graduated with a grade 12 IPP. I must note, that although he had such severe learning difficulties, there were times he was unable to absorb any material, but every so often there were times that he had learning spikes, being able to learn rapidly. In his own words, "I will never learn to read" This shouldn't be listened to by parents, since by encouraging constantly even when you think nothing else can be learned, it can. He as an adult now reads more fluently than most college graduates. He is still, however struggling, yet learning to spell. ❞ - Age 28

## Speech, communication and sociability

The abilities to learn and to be sociable are strongly associated with the abilities to understand and use language. Half of all Unique members with a 15q11.2 microduplication, and no other known genetic change, informed us that their child with a 15q11.2 microduplication had or has delayed speech. All families bar one who completed the Unique survey noted that their child had speech and language difficulties. Delayed speech and speech apraxia (when a child has difficulty translating conscious speech plans into motor plans) were noted. A number of families mentioned their child did not begin to speak until age 5.

Twelve families noted their child as having absent speech above the age of 18 months, but only one family mentioned absent speech after the age of 5 (a few words spoken at age 8 years).

Parents also mention that their children's comprehension of language is considerably better than their ability to communicate using language and they had difficulties understanding humour, abstract concepts, non-literal or figurative language (where the meaning of the conversation does not correspond exactly to the meaning of each word). Children can also show difficulties with appropriate language use in social situations (pragmatic speech).

An assessment by a speech and language therapist should be able to identify specific difficulties and regular therapy sessions should be tailored to a child's specific areas of need. While behaviour and sociability are affected by language abilities, other neurodevelopmental behavioural difficulties may also be involved (as described in the following section).

**"** We knew she was learning all along, but we didn't realize how much she had been learning (colors, shapes, letters, etc.) until we got her talker/AAC device and she was able to tell us. **"** - Age 4

**"** We had 5 words by 18 months that then disappeared. Lots of babble and speech only really beginning to come through at age 5 1/2. Lots of sounds still cannot be made but understanding of speech is fine. Tries and wants to speak now but can be hard to understand at times. **"** - Age 5

**"** The main issue is his speech delay. He tries hard to be social but often cannot be understood which eventually leads to frustration. He is tall for his age so many other children cant understand why he has limited speech. He doesn't understand social cues or non verbal signs of communication. **"** - Age 5

**"** She is non verbal. Operates around that of an 18 month old. Only says a few words intermittently. However, her understanding has improved considerably. I think she understands everything. **"** - Age 8

**"** She finds it difficult to communicate especially in social situations. She still remains non-verbal with the occasional word. At times she gets very frustrated and angry that she can't make herself understood. However, her non-verbal communication has improved in the last few years and having a couple of signs of Makaton (more and please) transformed her life. **"** - Age 8

**"** He really struggles in social situations, we try to avoids busy places or having to interact with crowds or new people. He is not sure how to start, maintain or end a successful conversation if it is not on his preferred subjects . **"** - Age 10

**"** He was speaking putting two words together at 18 month and developed conversational speech. He lost all language at aged 2 years 9 months. **"** - Age 6

**"** Although he cannot speak he is good at communicating his needs to people close to him. He uses some makaton and pictures to help him communicate. He also uses body language and facial expressions. Or takes you to certain items he needs help with or will bring items to you that he needs your help with. He also points to objects of interest. **"** - Age 3

“ He has great difficulty communicating with others in a social setting. He is very soft spoken and kind. He has a tough skin and has always been made fun of. He reacts very well to everyone having their differences, not just him. He has to be reminded to interact with people. ” - Age 25

## Behaviour

Not all children or adults with a 15q11.2 microduplication have behavioural difficulties, but as a group, they appear to show a higher incidence of behavioural, social and communication difficulties. It is not yet known exactly what causes this but a known vulnerability in this area means that children should be monitored and families offered early support. Diagnoses that have been reported in some people with a 15q11.2 microduplication are as follows:

- ASD: Autism or Autism spectrum disorder
- ADHD: Attention deficit hyperactivity disorder
- OCD: Obsessive compulsive disorder
- SPD: Sensory processing disorder
- PDD-NOS: Pervasive developmental disorder—not otherwise specified
- Anxiety

Other reported behaviours include autistic like behaviour, aggressive outbursts and mild self harming. Some behaviours may be anxiety based due to other difficulties in areas such as comprehension and communication.

From birth to at least 3 years of age, most children are routinely screened for developmental milestones. If there are any concerns about a child’s development (either from the doctor or a parent or carer) they should be referred for developmental evaluation, which may include a hearing test and autism specific screening.

There is not a ‘medical test’ that can diagnose autism, 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.

Seventeen children with a 15q11.2 microduplication known to Unique have been given a diagnosis of autism or autistic spectrum disorder. Two families mentioned their child had undergone an autism specific evaluation due to autistic like behaviours but no autism or ASD diagnoses were given, other families are awaiting assessment.

Autism is a spectrum disorder meaning that the same diagnostic ‘name’ is given for a number of different but closely related disorders. If a child doesn’t ‘tick enough boxes’ to fall into the spectrum they may be described as having autistic

like behaviour. The reasons for such behaviour are not always understood but are thought to have a neurological basis.

❝ He has a diagnosis of autism, he needs constant support with everyday life, he sees the Additional Support for Learning teacher to help in school for academic as he is 2 years delayed across the whole curriculum. Instructions need to be simple and short and be constantly repeated. He has poor social skills and will work on his own better than in a team. ❞ - Age 10

❝ Socially, he doesn't mind being around other people. At nursery he sometimes attempts to interact by getting close to peers and copying actions. He sometimes holds peers hands on way to lunch. He likes to be in the centre of group time. Sometimes he blanks people he doesn't know. ❞ - Age 3

❝ He is a loving boy with who he chooses to be. He has very funny and loves making people laugh. If given 1:1 attention at all times he copes well but he can lose his temper very quickly which can result in violent outbursts. This usually stems from not being understood/listened to or having to wait for something or plans changing unexpectedly. He has fleeting attention and is constantly on the go. ❞ - Age 5

Some children with 15q11.2 microduplications are described as having a sensory processing disorders (SPD). This means they have difficulties processing sensory input which can lead to behavioural difficulties as well as affecting social interactions and learning abilities. While most professionals diagnose and treat SPD nowadays, not everyone is aware of this neurological disorder. If you think your child has an unusual reaction to sight, sound, touch, taste and smell, they may have an SPD that may be affecting their behaviour. Movement, balance and body position can also be affected.

❝ Typically she is a curious and sweet child. She enjoys going to school and therapy. She has an ASD diagnosis and sensory processing disorder (touch). ❞ - Age 4

❝ He was recently diagnosed as being autistic. He is very sensitive to touch - loves all soft fabrics.' He uses aromatherapy oils to help with frustration. Noise- hates being is crowded places. Clothing– tags have to be cut off and he will only wear jogging trousers, he has 1 pair of jeans which have an elastic waist and only wears for special occasions. Lights- prefers to have lamps on. ❞ - Age 10

❝ No SPD diagnosis but definitely displays many sensory issues. He is particularly sensitive to temperature. As a baby and toddler, food had to be cold and bath water had to be just room temperature. He still cant stand being hot but has improved with food. He is very sensitive to sound and smells. ❞ - Age 5

❝ He mostly has good days. Wakes up happy even though I have to wake him for school. Cooperates at school most of the time. ❞ - Age 8

❝ He attends a special needs school and they are incredibly supportive and often putting different levels of support in place. We as parents have attended behaviour workshops which have been helpful too. ❞ - Age 5

Children with behavioural difficulties may benefit from specialist therapy such as that provided by a speech and language therapist (SALT) and occupational therapists (OT) but families have also mentioned their use of BT (behavioural therapy), ABA (applied behaviour analysis) therapy, hippo therapy (horse riding), music therapy and RDI [relationship development intervention (helping children to develop different aspects of social connections)].

“ He is in behavioral therapy 2 times a week. ” - Age 10

Recent research has also identified a genetic association of 15q11.2 microduplications with anorexia nervosa (AN, Chang 2019) and major depressive disorder (MDD, Zhang 2019) although associations cannot be classified as statistical significant. A number of Unique members also mentioned their child suffered from anxiety.

## Pain Threshold

It is not unusual for families of children with neurodevelopmental differences to note that their child appears to have a higher pain threshold than ‘normal’. 14 out of the twenty families who responded to the Unique survey noted that their child with a 15q11.2 microduplication appears to have a high pain threshold, which means they appear to be less sensitive to pain. Although the point at which a person perceives a stimulus as painful varies between people and over time, it’s possible that some people may have an altered pain sensitivity.

## Puberty

There is limited information available about puberty in children with a 15q11.2 microduplication although, at the time of writing, Unique had 5 members with a child aged between 12 and 18 with a 15q11.2 microduplication and no other known genetic variation. One family mentioned their child entered puberty early, but this also occurs in children with no known genetic anomalies.

## Adults

When this guide was written in 2019, Unique had 1 adult member, aged 22, with a 15q11.2 duplication of the Burnside-Butler region. They were referred to the DDD (Deciphering Developmental Disorders) project in the UK to find an alternative genetic explanation for their neurodevelopmental difficulties. Another adult member, aged 20, has a duplication of the SNRPN gene.

Unique also has a number of unaffected or mildly affected adults identified as having a 15q11.2 microduplication as a consequence of their child’s investigation, they were otherwise unaware of their duplication.

# Medical concerns

The most commonly reported medical causes of concern for children with 15q11.2 microduplcations are seizures. Other problems include recurrent respiratory infections in childhood but most families report that their child with an interstitial 15q11.2 microduplication is consistently in generally good health. No common unusual findings from routine blood tests have been reported.

“ In the 1st 3 years he had many chest infections and ear infections but it seems to have lessened now. ” - Age 5

## Seizures

Ten Unique families have informed us that their child with a 15q11.2 microduplication has seizures (a sudden change in electrical activity of the brain that causes momentary brain dysfunction). Many families reported that their child had no signs of any seizure activity (with ages ranging from baby to adulthood).

Reported seizures types vary and include absence seizures (affects both sides of the brain, awareness of surroundings or actions are momentarily lost), infantile spasms, tonic myoclonic (loss of consciousness with rigidity of the body (tonic) and then sudden jerk like movements (myoclonic), complex focal seizures (does not affect the whole brain, awareness of surroundings or actions are momentarily lost), when seizures are recurrent they are described as epileptic. The age at which seizures start varies but, in people with 15q11.2 microduplications, most start before adulthood and often only a few seizures occur, or seizures stop after a certain amount of time.

“ Seizures changed from infantile spasms to tonic and myoclonic over time. Treatment of seizures: Cyclobenzaprine. ” - Age 28

“ Regular seizures, absent and clonic. Daily medication at max dose now. Making some improvement. ” - Age 2

“ She has occasional complex focal seizures. The first neurologist didn't believe she was having seizures because her EEG's were normal. It took us 3 years to finally get her diagnosed with epilepsy, after getting a 7 minute "episode" on video and showing to a new neurologist who specialized in seizure disorders. She immediately recognized it as complex focal seizure. ” - Age 6

“ Seizures began around age 13 months. Initially the doctors put him on Keppra pending an EEG result. EEG showed infantile spasms consistent with West Syndrome. They then changed his medication to prednisalone steroid (for 2 weeks) 4 times a day and vigabatrin 2.5ml twice a day (indefinitely). No noticeable seizures since the new medicine. ” - Age 2

“ He was born with severe Tremors in his head. They would last 30-45 seconds every minute to minute and a half. They started to happened the moment he was born and went away around 9 months or so. ” - Age 2

“ He has a slowing in his left temporal lobe and takes carbamazepine. ” - Age 6

## Gastrointestinal problems

Food consumption and passage can be affected in a number of ways at any point of this complex process. About half of Unique members who provided information about feeding mentioned difficulties during the first few months, with frequent mention of reflux, but problems resolved during childhood. A few families mentioned their child was tube fed at a young age and developed into being a picky eater. Several families mentioned their child was constantly hungry but gastrointestinal problems do not appear to be a common feature of 15q11.2 microduplications.

Some children with a 15q11.2 microduplication have reflux (gastroesophageal reflux (GERD) when food returns up the foodpipe) and vomiting. There are many different reasons why this can occur (e.g. trouble swallowing, delayed emptying of the stomach, sphincter is too tight, blockage) so it is important the correct diagnosis is made to enable the most appropriate choice of treatment.

Constipation was reported in a number of children and can be due to many different reasons. It is important to identify the possible cause of the constipation and if treatment is needed, the use of a low dose of stool softener when necessary is recommended.

## Eyes and vision

Although eye and vision problems are not commonly reported in association with 15q11.2 microduplications, seven families have reported that their child has an eye or vision problem. Three families informed us their child is long sighted and one severely short sighted. Two children have a strabismus (misaligned eye), three have an astigmatism (blurred vision that may be due to curvature of the cornea or lens). Two children were identified as having eye tracking/scanning difficulties, another had retinal detachments. One child was diagnosed with cortical visual impairment, where sight is affected due to the relevant part of the brain not functioning correctly as opposed to the eyes not functioning as they should.

## Ears and hearing

Several Unique members have mentioned that their child with a 15q11.2 microduplication suffered numerous ear infections when young. Having frequent ear infections can be annoying and painful for a child and commonly necessitates use of antibiotics. Children can be fitted with ear tubes to equalise the air pressure either side of the eardrum and to improve hearing. Glue ear (when the middle ear becomes filled with fluid) and the consequent effect on hearing at a stage crucial for language development can be frustrating for a child. Permanent hearing problems are not commonly reported in association with this microduplication.

## Teeth

It is not uncommon for children with chromosomal changes to have problems with dentition. Although no consistent unusual dental anomalies have been observed in children with an interstitial 15q11.2 microduplication, many families

mentioned their child grinds their teeth. A few families mentioned their child was late teething, and a few mentioned early decay. One family mentioned their child developed an extra set of teeth, and one mentioned hypoplasia, where the teeth have insufficient enamel coverage.

### Bones, joints and spine

Bone and joint problems do not appear to be a common feature of 15q11.2 microduplications. Three Unique members mentioned their child has scoliosis (curvature of the spine). Nine families mentioned their child had joint hypermobility (joints that move beyond the expected range). Joint hypermobility often has no symptoms but can result in pain.

## Families say ..... things our children love to do ....

“ She loves to do puzzles, listen to music, ride on her Minnie ride-on toy and color. She also loves water and being in the pool. ” - Age 5

“ He loves to draw. Loves letters and numbers. Toy animals. Loves trains and the YouTube kids. In the last 3 months I think his interest in letters and numbers has improved significantly and is quite advanced for his age. Nursery have also mentioned this. ” - Age 3

“ He loves being outdoors but due to his lack of danger awareness and escaping tendencies this can be tricky at times to find appropriate places to go. He loves swimming. This can also be difficult due to escaping but he really enjoys being in the water. He loves painting and any sort of messy play. He doesn't really enjoy many writing activities although he will enjoy some colouring. However due to his fleeting attention span this is only ever for 5/10 minutes. ” - Age 5

“ She loves music. She doesn't sing along with music but listens carefully and then sings the tunes back to herself later. Loves being outside and being in nature. ” - Age 8

“ He enjoys playing games on his phone or computer and keeps up with the news. He likes to eat, play with the kitty, going for coffee with his brother, watching stock market trends (watching patterns), sitting and talking with family. ” - Age 28

## Family advice .....

“ I couldn't find any network with his Chromosome disorder until I contacted Unique so I thank you for your support and your Facebook cafe is where I found other parents with children with the same as my child who suggested joining the microduplication 15q11.2 Facebook group. It's the only place that has families with only the micropduplication. This is a must group. Don't be afraid to ask for support or advice on the group everyone is friendly. ”

“ Please don't listen to doctors who tell you that your child will never do this or that. Had I done that, my son would be in a wheelchair, totally blind, and put in a special classroom setting or institution where he would never have learned and succeeded to the best of his abilities. ”

❝ I just want families with this condition to know that against all odds, or regardless of adversity or situations in life, this condition which is poorly understood by doctors (at this time) requires patience, and unending amounts of dedication to your child. If your child tends to be a very literal and logical thinker, views jokes and sarcasm as lies, please understand this is a part of their condition. Don't listen to everything the doctors tell you on what the limitations are of your child. Their limitations are only a construct of what you make them to be. ❞

❝ Go with your parental gut because doctors don't know enough about this condition to give good advice. ❞

❝ My biggest piece of advice is to not let a diagnosis scare you. I feel fortunate we didn't know my son had dup15q11.2 syndrome until he was a little older because I would have been very afraid of the what if's', and questions of how bad he would be affected. On the other hand not knowing why everything was happening was very scary too. Take one day at a time and the sky is the limit. My son may be different, he may have had struggles but he is happy. He hopes to be an advocate for those with developmental disabilities and he wants to help others suffering from depression and anxiety. Take one day at a time and enjoy every small milestone, they grow up to fast. If I had to do it all over again...I would in a second, Duplication 15q11.2 and all. He's a wonderful young man and I'm very proud. ❞

## Duplications and genes

This section provides further information about important genes included in 15q11.2 microduplications.

### Burnside-Butler region

The four most significant genes found in the 15q11.2 Burnside-Butler region are known as *NIPA1*, *NIPA2*, *CYFIP1* and *TUBGCP5*. Although it is unclear what symptoms may be related to duplications, there is information associated with deletions or variants of each gene. These genes are not imprinted which means both copies are active (those inherited from both the mother and the father).

The *NIPA1* (non-imprinted in Prader-Willi/Angelman syndrome 1) gene has been associated with progressive stiffness and contraction in the lower limbs and postural disturbance (Rainier 2003; Chen 2005; Goytain 2007; Rainier 2012). This gene is also known to mediate magnesium (Mg2+) transport and is highly expressed in the brain (Goytain 2007).

*NIPA2* (non-imprinted in Prader-Willi/Angelman syndrome 2) also plays a role in magnesium transport (Goytain 2007) and this gene has been linked to childhood absence epilepsy (Jiang 2012).

The *CYFIP1* (cytoplasmic fragile X mental retardation 1 *FMR1* interacting protein 1) gene codes for a protein that interacts with another protein called FMRP that has been associated with fragile X syndrome (FXS). These two genes play important roles in the regulation of other genes in the brain (Bozdagi 2012; de Wolf 2013).

The *TUBGCP5* (tubulin gamma complex associated protein 5) gene has been associated with attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) (de Wolf 2013).

Studies using cells from people with the Burnside-Butler 15q11.2 microdeletion showed abnormalities of dendritic spine (parts of neurons that help transmit electrical signals) formation indicating a role in neurodevelopment (Das 2015).

## *MAGEL2* and *NDN*

Alterations to the *MAGEL2* (*MAGE* family member *L2*) gene causes a neurological disorder called Schaaf-Yang syndrome, symptoms include global developmental delay/intellectual disability, sleep apnoea, hypotonia and feeding difficulties during infancy. Some children with *MAGEL2* alterations have autism spectrum disorder (ASD). *MAGEL2* has also been associated with congenital arthrogryposis multiplex, which is when babies are born with two or more joint contractures (curvatures). A microduplication containing this gene has been associated with autistic behaviour, global developmental delay and delayed speech and language development.

This gene is maternally imprinted which means, only the copy inherited from the father is active, the copy inherited from the mother is 'silenced'. The paternal copy of this gene is active in several fetal tissues including the brain (Boccaccio 1999, Lee 2000). Possible symptoms caused by a duplication of this gene would hence only be expected if the gene inherited from the father was duplicated.

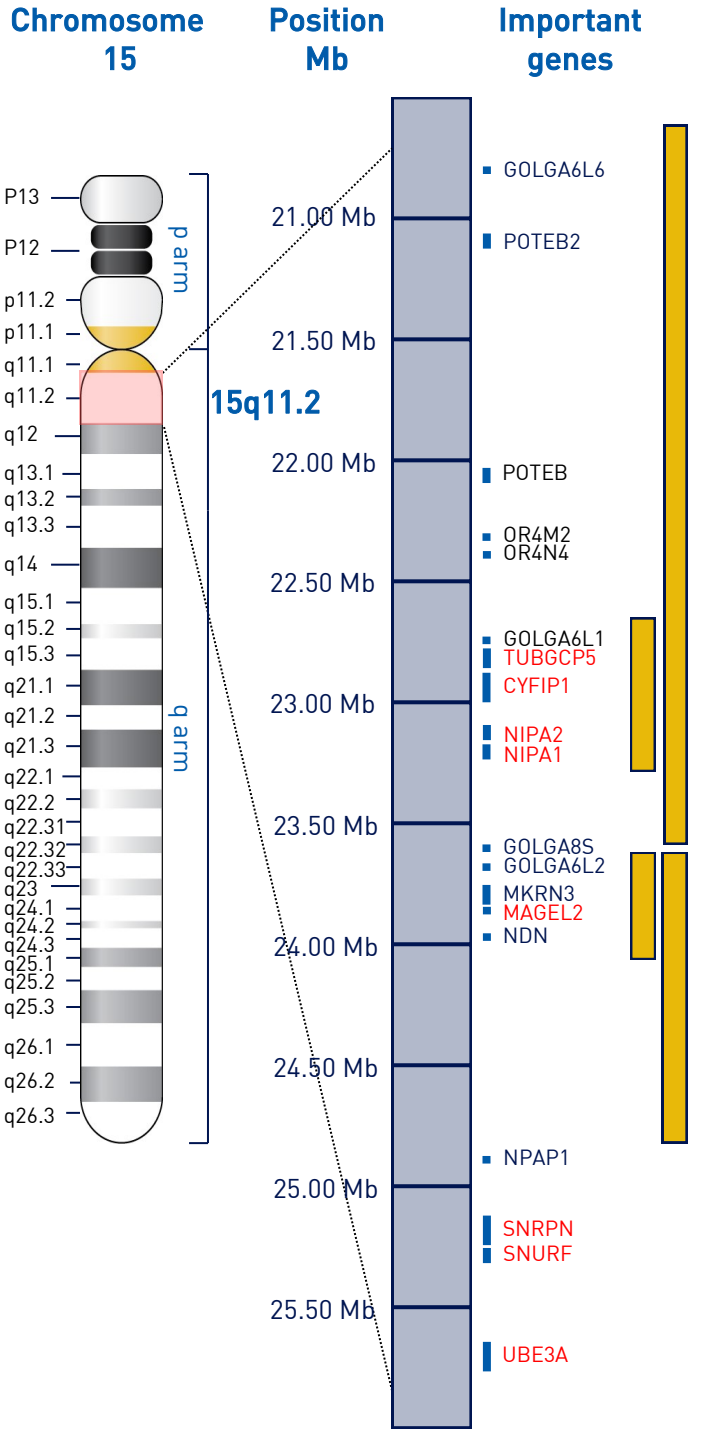
The situation is similar for *NDN*, another maternally imprinted gene important for proper neurological function (MacDonald and Wevrick 1997, Jay 1997, Nakada 1998, Gerard 1999, Muscatelli 2000, Lee 2005).

## *SNRPN* and *SNURF*

*SNRPN* (small nuclear ribonucleoprotein polypeptide N) and *SNURF* (*SNRPN* upstream reading frame) genes overlap each other, which means some of the information (coding DNA sequence) they use is the same. *SNRPN* is maternally imprinted so only the gene inherited from the father is active, and is highly expressed in the brain and heart (Rodriguez-Jato 2005). *SNURF* is also maternally imprinted. Unique has one member with a duplication of the *SNRPN* gene who has developmental delay, intellectual impairment and a congenital heart defect.

## *UBE3A*

The *UBE3A* (Ubiquitin-protein ligase E3A) gene shows a varied imprinted pattern, the gene inherited from the mother is expressed in the neurons of the embryonic brain (Dindot 2008) but the gene inherited from either parent can be expressed in glial cells (Yamasaki 2003). Duplications of this gene have been associated with expressive language delay, global developmental delay, incoordination and morphological abnormality of the central nervous system. Mouse studies have shown that an increase of UBE3A decreases the activity of a gene important for sociability (Krishnan 2017) and increases anxiety-like behaviours and learning impairments as well as reducing seizure thresholds (Copping 2017)




This diagram was generated using Human genome build GRCh37/hg19 which was released in February 2009. If your genetic report was issued prior to this (e.g. hg18) or following the publication of this guide (e.g. hg38) the position of your duplication may have changed slightly.

These are examples of the most common duplications. They can vary in size but all contain the **TUBGCP5**, **CYFIP1**, **NIPA2** and **NIPA1** genes often referred to as the **Burnside-Butler** region.

These are examples of less commonly identified microduplications. They vary in size but all contain the **MAGEL2** gene.

Unique currently has one member with an **SNRPN** duplication and one family with a larger duplication that includes **NDN**, **SNRPN**, **SNURF** and **UBE3A**.

## Inform Network Support

**Rare Chromosome Disorder Support Group**
The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Understanding Chromosome & Gene Disorders

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 http://www.rarechromo.org/html/donate Please help us to help you!

## Websites, Facebook groups

http://www.dup15q.org/Dup15q
Dup15q Alliance provides family support and promotes awareness, research and targeted treatments for chromosome 15q duplication syndromes.

Microduplication 15q11.2 Parent Support:
https://www.facebook.com/groups/1482240128719818/

15q11.2 Advocacy, Research, and Support:
https://www.facebook.com/groups/1419874888238714/

Duplication 15q11.2 Network:
https://www.facebook.com/15q112/

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 compiled by Unique (AP) and reviewed by Professor M. G. Butler M.D., Ph.D., Division of Research and Genetics, Director KUMC Genetics Clinic, Professor of Psychiatry, Behavioral Sciences and Pediatrics, ABMG Certified Clinical Geneticist and Clinical Cytogeneticist, Department of Psychiatry and Behavioral Sciences, School of Medicine, The University of Kansas Medical Center, Kansas City, Kansas, USA.

Version 1 2019 (AP)



Rare Chromosome Disorder Support Group
Registered in England and Wales
Charity Number 1110661
Company Number 5460413