Inform Network Support

Understanding Chromosome & Gene Disorders

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

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This leaflet 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. The information is believed to be the best available at the time of publication. It was compiled by Unique and reviewed by Dr Girisha KM, Kasturba Medical College, India.

The CAKUT (congenital anomalies of kidney and urinary tract) information in this guide was updated in 2021 by Dr. Emily Groopman, MD/PhD (Broad Institute of MIT and Harvard, Cambridge, MA, USA; Boston Children's Hospital, Boston, MA, USA)

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17q12 microduplications

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Sources and references

The information in this guide is drawn partly from the published medical literature. The first -named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih .gov/pubmed/). If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from a survey of members of Unique conducted in 2013, referenced Unique. When this guide was written in May 2013 Unique had 11 member families with a microduplication of 17q12 ranging in age from a 2-year-old to two adults. Four further members had a 17q12 microduplication as well as another chromosome deletion or duplication.

17q12 microduplications

A 17q12 microduplication is a rare genetic condition caused by a tiny extra part of one of the body's 46 chromosomes – chromosome 17. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Even a tiny piece of extra material can disrupt development.

Background on Chromosomes

Chromosomes are structures found in the nucleus of the body's cells.

Every chromosome contains thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information telling the body how to develop, grow and function. Chromosomes (and genes) usually come in pairs with one half of each chromosome pair being inherited from each parent.

Humans have 23 pairs of chromosomes giving a total of 46 individual chromosomes.

Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short or petit (p) arm (shown at the top in the diagram on page 3) and a long (q) arm (the bottom part of the chromosome).

Chromosome Duplications

A sperm cell from the father and an egg cell from the mother each carries just one copy of each chromosome. When they join together they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes can break off or become arranged differently from usual. People with a 17q12 have two intact chromosome 17s, but also an extra piece (duplication) from the long arm of chromosome 17. Therefore it is believed that most of the clinical difficulties are probably caused by having only three copies (instead of the usual two) of a gene or number of genes from the extra piece. We are still learning about the specific jobs or functions of the genes in this region. It is important to keep in mind that a child's other genes, environment and unique personality also help to determine future development, needs and achievements.

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I wish.....

"We'd known that the doctors don't know everything. We were told that he would be significantly delayed in all areas and that he may never do some of the things he can do. He has surpassed every expectation his medical team has given him, and he continues to thrive and do well."

Families say.....

"He has taught me patience, love and understanding. I am so lucky to be his mom."

"He is loving. If he gets cross you can give him a cuddle and he soon forgets."

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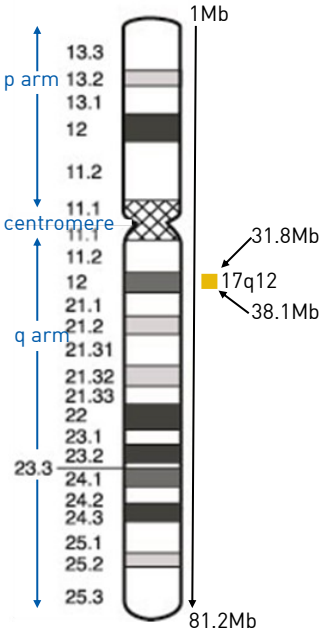
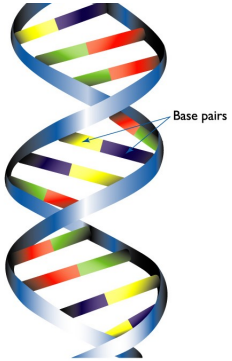
Looking at 17q12

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. You can see these bands in the diagram of the long arm of chromosome 17 to the right. Band 17q12 contains around 6.3 million base pairs. This sounds a lot but it is actually quite small and is only 0.2 per cent of the DNA in each cell and only 8 per cent of the DNA on chromosome 17. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure.



People who have extra chromosome material are said to have a duplication but when the amount is so small that it can't be seen even under a high-powered microscope, it is called a microduplication. The 17q12 microduplication can often only be found using molecular or DNA technology, in particular a technique using microarrays (array-CGH), that shows gains and losses of tiny amounts of DNA throughout the genome and can demonstrate whether particular gene(s) are present or not. The microduplication involving 17q12 is usually 1.4-1.8 Mb in size and encompasses 20 genes.



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

Genetic Report

Your geneticist or genetic counsellor will be able to tell you about the changes found in your child's chromosomes. With a 17q12 microduplication, the results are likely to read something like the following example:

arr[hg19] 17q12 (34,815,551-36,180,571) x3

arr	The analysis was by array (arr) comparative genomic hybridisation (cgh)
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted
17q12	The chromosome involved is 17 and part duplicated in band q12
34,815,551-36,180,571	The base pairs between 34,815,551 and 36,180,571 have been duplicated. Take the first long number from the second and you get 1,365,020 (1.4 Mb). This is the number of base pairs that are in the duplication
x3	means there are three copies of these base pairs, not two as you would normally expect

17q12 microduplications

The first published description of a person with a 17q12 microduplication was in 2006. There have since been around 20 cases reported in the medical literature worldwide. The duplication occurs equally often in boys and girls (Sharp 2006; Mefford 2007; Mencarelli 2008; Nagamani 2010; Faguer 2011; Brandt 2012; Bierhals 2013).

17q12 microdeletions

Many more people have been described with a different disorder known as 17q12 microdeletions where the same piece of band 17q12 is not extra but is missing. Unique publishes a separate information guide to 17q12 microdeletions.

How much do we know?

Comparing different children and adults with 17q12 duplications shows that some effects seem to be very broadly similar. This information guide tells you what is known about those effects. Comparing your child's array results with others, both in the medical literature and within Unique, can help to build up a general picture of what to expect. But there will still be differences, sometimes quite marked, between your child and others with an apparently similar array result. It is very important to see your child as an individual and not to make direct comparisons with others with the same chromosome test results. After all, each of us is unique.

Most common features

Every person with a 17q12 microduplication is unique and so each person will have different medical and developmental concerns. Additionally, no one person will have all of the features listed in this information guide. However, a number of common features have emerged:

- Children often need support with learning. The amount of support needed by each child will vary
- Speech and language delay
- Behavioural difficulties
- Seizures, in some but not all
- Otherwise generally healthy

Are there people with a 17q12 microduplication who are healthy, have no major birth defects and have developed normally?

There are many individuals with the microduplication who appear normal and have no major birth defects, all of whom only discovered they had the duplication when it was detected in their children. Both fathers and mothers have passed the microduplication on to their children (Sharp 2006; Mefford 2007; Mencarelli 2008; Nagamani 2010; Faguer 2011; Bierhals 2013; Unique).

In families where the 17q12 microduplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 17q12 microduplication rises to 50% in each pregnancy. However, the effect of the microduplication 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.

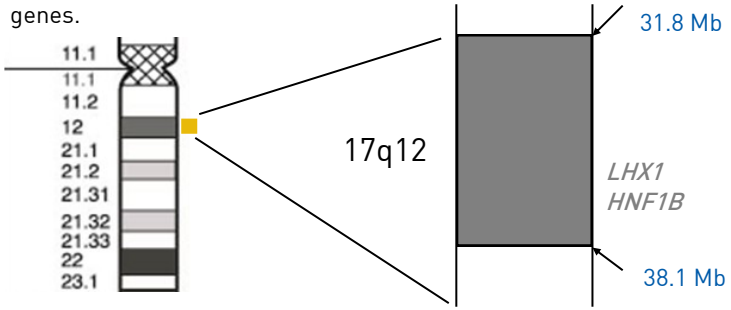
Will my child have similarly affected children?

It is too early to know whether this duplication affects fertility. However, there are quite a few reports of people with a 17q12 microduplication having children so it is likely that fertility is normal. In each pregnancy, someone with the microduplication is likely to have a 50 per cent risk of passing it on and a 50 per cent chance of having a child without it. We haven't known about this microduplication for long enough to be certain of the range of possible effects or how obvious they will be.

Growing up with a 17q12 microduplication

Research involving 17q12

The microduplication involving 17q12 is usually 1.4-1.8 Mb in size and encompasses 20 genes.



People who have a change in or are missing the gene *HNF1B* (at position 36,046,434-36,105,096) are at risk of having renal anomalies and so this gene when duplicated may be responsible for the kidney anomalies that affect some people who have a 17q12 microduplication. It has been suggested that this gene may also play a role in autism (Loirat 2010).

LHX1 (at position 35295757-35298691) is a candidate gene for the neurocognitive features of a 17q12 duplication. *LHX1* is expressed in the brain during early development (Nagamani 2010).

It is important to remember that while identifying the gene(s) responsible for certain features of the 17q12 microduplication syndrome is valuable and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is extra, it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

How did this happen?

In some cases the 17q12 microduplication was inherited from a parent (Unique, Mefford 2007; Mencarelli 2008; Nagamani 2010; Faguer 2011; Bierhals 2013; Unique).

In some people the 17q12 duplication has occurred out of the blue for no obvious reason. The genetic term for this is *de novo* (dn) and a blood test shows that both parents have normal chromosomes. *De novo* 17q12 microduplications are caused by a mistake that is thought to occur when the parents' sperm or egg cells are formed or in the very earliest days after fertilisation.

What is certain is 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 17q12 microduplications. There is nothing that either parent did before or during pregnancy that caused the microduplication.

Can this happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 17q12 microduplication 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 the 17q12 microduplication. 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.

If one person in a family with the 17q12 microduplication is mildly affected, will others in the same family also be mildly affected?

Not necessarily. There is a lot of variation between different members of the same family who have the same microduplication. We know that if one person is mildly affected or unaffected, others may be more severely and obviously affected (Mefford 2007; Mencarelli 2008; Bierhals 2013; Unique).

What is the outlook?

We can't be certain yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan and there are a number of adults both at Unique and in the published medical literature.

Pregnancy and birth

Many pregnancies were uncomplicated, and babies were born at or near their expected due date.

Many mothers (6/11) carrying babies with a 17q12 microduplication experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, pregnancy complications in mothers carrying a baby with 17q12 microduplication have been reported. Two babies were smaller than expected resulting in one having frequent growth scans although she was subsequently born with a healthy weight. The second baby was later diagnosed with an echogenic bowel (the bowel looks white rather than grey and speckled on a prenatal ultrasound scan) at 18 weeks. His mother also had pregnancy induced hypertension (high blood pressure). One baby showed less fetal movement than expected while in the womb. One baby was delivered at 33 weeks by C-section performed after placental abruption (the placenta separates from the wall of the uterus before birth). One mother had polyhydramnios (an unusually high volume of amniotic fluid) (Nagamani 2010; Brandt 2012; Bierhals 2013; Unique).

Range of birth weights (at or near term):

2.7 kg (5lb 15oz) to 3.9 kg (8lb 11oz)

Where birth weights are known, they are all within the normal range, with an average of 3.18 kg (7lb). Two babies were born early (before 36 weeks) (Nagamani 2010; Bierhals 2013; Unique).

Feeding and growth

Feeding and growth does not seem to be affected in children with a 17q12 microduplication

The majority of children with a 17q12 microduplication have normal growth. However, one Unique baby was described as 'failure to thrive' (slower growth than expected) and another Unique member was growth hormone deficient (Unique).

Feeding problems have not been described in the medical literature but have been seen in several Unique members. The hypotonia (low muscle tone) that is common in babies with a 17q12 microduplication may lead to difficulties with sucking and swallowing, and/or latching onto the breast. The floppiness can also affect their food pipe and contribute to gastro-oesophageal reflux (in which feeds return readily up the food passage). This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head end of the bed for sleeping. If these measures are not enough, feed thickeners and prescribed medicines to inhibit gastric acid may control reflux but some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage. Three Unique babies benefited from having a temporary nasogastric tube (NG-tube, passed up the nose and down the throat) and/or a gastrostomy tube (a G-tube, feeding direct into the stomach) (Nagamani 2010; Brandt 2012; Bierhals 2013; Unique).

> "He had severe feeding issues from birth. He was unable to latch on to breastfeed and was aspirating, but we fed him very small amounts with a syringe. He had an NG-tube and subsequently a G-tube at 10 months old. Type I laryngeal cleft [a gap between the food-pipe and windpipe] diagnosed and repaired. He received breastmilk only via tube for the first 12 months due to his inability to handle solid foods. He frequently vomited his feeds (several times daily) and had severe reflux from birth onwards. He was diagnosed with a sensory processing disorder at 12 months due to hypersensitive gag reflex/issues with food consistency and texture. He was G-tube dependent until 18 months but is now independent of G-tube at 34 months – only using it for medications and hoping to remove it in a few months. Treatments he has received for feeding issues include speech therapy, feeding/swallowing therapy and occupational therapy" – 34 months

> "Her initial swallow reflex was delayed. She was fed by a nasal gastric tube for 9 months followed by a gastrostomy tube. She had a Mickey button [a type of G-tube] at 18 months until she was 6 years" – 7 years

> "He was breastfed for the first 8 weeks" – 7½ years

Health matters

Seizures

Six people with a 17q12 microduplication have had seizures. The age of onset of seizures is variable: from 7 months through to 7 years old. The seizure types are also varied (Mefford 2007; Faguer 2011; Bierhals 2013; Unique).

Kidneys

Kidney (renal) anomalies have been reported and include: absent kidney/s (renal agenesis); small kidneys (renal hypoplasia), which can also have abnormal tissue (renal hypodysplasia), such as cysts (cystic dysplasia); posterior urethral valves, extra flaps of tissue in the urethra (the tube that drains urine from the bladder), which can block urine from flowing out (from the urethra into the bladder); duplicated collecting system, where instead of having the (usual) one ureter (the tube that carries urine from the kidney to the bladder), a kidney has two ureters; and vesicoureteral reflux, where urine flows backwards, from the bladder towards the kidneys (Faguer 2011; Brandt 2012; Bierhals 2013; Mitchel 2016; Verbitsky 2019; Unique).

Oesophageal atresia

Oesophageal atresia (a birth defect in which there is a blind ending oesophagus [food pipe] which requires surgical correction) has been reported in two people (Nagamani 2010; Faguer 2011).

Constipation

Constipation has been described in some children with this microduplication. Dietary changes and/or medication can help to manage the problem (Brandt 2012; Unique).

Eyesight

Two people had a squint (where the eye turns inwards, outwards, up or down). One person reported in the medical literature had microphthalmia (very small eyes), Peter's anomaly [an eye disorder involving thinning and clouding of the cornea (the clear cover over the iris and pupil) which causes blurred vision] and glaucoma (an eye condition in which the optic nerve is damaged due to changes in eye pressure) (Mencarelli 2008; Bierhals 2013; Unique).

Hearing

Generally speaking children have had normal hearing, although two young children had the fluctuating temporary hearing loss caused by a build-up of fluid behind the eardrum (glue ear), but they outgrew this naturally. If glue ear is severe or persistent, tubes (grommets) may be inserted into the eardrum to aerate the space (the middle ear) behind it and improve hearing (Brandt 2012; Bierhals 2013; Unique).

Heart

Cardiac problems have been rarely reported. Two children had small holes in the muscle wall of the heart (holes often close spontaneously by themselves but can be corrected surgically if necessary) (Mencarelli 2008; Unique).

Other

Other health concerns which may or may not be linked with the microduplication (because they have only been reported in one person) include asthma; clubfoot (talipes); osteopenia and joint laxity (looseness or instability of the joint also called hypermobility or double jointedness); cleft soft palate (Bierhals 2013; Mencarelli 2008; Unique).

“ Her behaviour is pretty demanding. From birth she has needed to be watched and attended to and that still happens although not as much although she still expects it to be the same. She is a happy to go with the flow child. She can be shy with new people but gets on with everyone ” – 7 years

“ He is very sociable, friendly and helpful. His all-time favourite thing is to watch TV. If you let him he would watch all day. He does like going out, his attention span is just not very long so he gets bored fairly quickly. He does have a lot of difficult and challenging behaviour. One thing is that he doesn't listen to instructions. He will rarely go and do something after being told once and you generally have to ask him about 3 times before you get any reaction. He also can be very awkward and he protests over everything (e.g. cleaning teeth, putting on shoes). He will not ever do it quietly; he has to make it difficult and protest about it. He is very active, he hand flaps very regularly and his body tenses and shakes. He finds it difficult to sit still and is very restless. He has few inhibitions with regard approaching strangers and will easily engage in conversation with anyone ” – 7½ years

Sleep

Sleep problems affect some children with a 17q12 microduplication. Some children take medication to help with sleep problems (Unique).

Appearance

Facial appearance

Children with 17q12 microduplication may have a subtle characteristic facial appearance.

Babies and children with this microduplication may have subtly different facial features that would not, however, make them stand out from a crowd of other children. Geneticists trained to note unusual features may find features such as upslanting eyes, a skinfold across the inner corner of the eye (an epicanthal fold), thick eyebrows or a unibrow (abundant hair between the eyebrows so they seem to form one long eyebrow) or a thin upper lip (Brandt 2013; Unique).

Hands and feet

Hand and feet anomalies do not appear to be common in those with 17q12 microduplication but one child has a second toe that overlaps the other toes and another child and his mother who both have the microduplication have mild syndactyly (fusion) of the second and third toes. The child also has mild syndactyly of the second and third fingers on both hands. One person has short fingers and toes (brachydactyly) with incurving little fingers (5th finger clinodactyly) (Mencarelli 2008; Nagamani 2010; Unique).

Motor skills (sitting, moving, walking)

Children with a 17q12 microduplication are often delayed in learning to sit and walk.

One of the causes of the delay in mobility in children with a 17q12 microduplication is low muscle tone, reported in a number of individuals. This makes a child or baby feel floppy to handle and generally improves and may disappear with physiotherapy and exercises. However, this means it may take a little longer for them to roll over, sit, crawl and walk. From the limited information that is available, sitting unaided is mastered between 9 months and 18 months (at an average of 1 year); crawling is mastered between 12 months and 2½ years (at an average of 20 months) and walking is mastered between 16 months and 2 years 8 months (an average of 2 years). However, a 5-year-old boy in the medical literature does not walk and can stand only with support (Casselli 2010; Nagamani 2010; Brandt 2012; Bierhals 2013; Unique).

“ He has difficulty climbing stairs but he is otherwise near age appropriate ” – 34 months

“ She walks, runs and does everything but is slower than the other kids ” – 7 years

“ He often walks or runs on tip-toe both indoors and outdoors. He scoots his scooter very well and he can climb and run, but he runs in a bit of a funny way. He cannot yet ride his bike but he is close to being able to do so and I think with more practice he will get there. He is a little bit clumsy and uncoordinated when doing detailed things. He cannot sit still and is always on the move ” – 7½ years

Fine motor skills and self-care

Fine motor skills may be affected in children with a 17q12 microduplication

Hypotonia can also affect fine motor skills in children with a 17q12 microduplication, and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles and cutting up food have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard or touch screen computer can often be easier. Toilet training may also be affected (Unique).

> “ He has minor issues with fine motor skills like holding crayons/feeding utensils ” – 34 months

> “ Her fine motor skills are better now but when she was younger she had a lot of trouble ” – 7 years

> “ He can hold cutlery but prefers not to, he would rather use his fingers. He can cut things out, but not as neatly as his peers ” – 7½ years

Learning

A 17q12 microduplication has a variable impact on learning ability, ranging from no impact to severe difficulties

Out of 13 people with a known level of learning, seven were described as having no learning disability; three were described as having a mild to moderate level of disability; one had a moderate learning disability and two have severe learning disabilities. Six further children were described as having an unspecified learning disability. A child with a learning disability is likely to need some learning support and many children benefit from attending a special educational school (Sharp 2006; Mefford 2007; Mencarelli 2008; Nagamani 2010; Brandt 2012; Bierhals 2013; Unique).

> “ His general development is age appropriate with no significant delays in any area at this time including cognitively. His strengths include memory, music and imaginative play. He loves puzzles/problem solving especially ” – 34 months

> “ She has a moderate learning disability. She loves music and remembers the words of songs she likes. She has a very good memory. She can draw and write her name. She needs easy, clear instructions and benefits from 1:1 attention ” – 7 years

> “ He started reading at 5½ years old. He does basic drawings but is improving. He gets special help every morning at school from a teaching assistant and the one to one support really helps as does constant guidance generally. He struggles with reading, spelling and numeracy. His recall of things he has learned is very variable. Some days he can remember things and the next day he seems not to know, for example spellings he will know perfectly one day and will not remember them all the next day ” – 7½ years

Speech and communication

Speech and language delay is common in children with a 17q12 microduplication

Speech and language development was delayed in most children, but it is not known whether the delay was in line with the child's cognitive abilities. Speech is variable in those with a 17q12 microduplication, with some people whose speech is not affected at all, but some who are non-verbal. Children have delays in both receptive (understanding) and expressive language (speech). A 3-year-old has a vocabulary of about 50 words; a 5-year-old has 5 words and pulls hands to desired objects; another 5-year-old has no speech (Mencarelli 2008; Nagamani 2010; Brandt 2012; Bierhals 2013; Unique).

> “ He started signing at 12 months, started talking around 17 months with single words but was able to use 2 word phrases at 27 months and now uses 2-4 word phrases and is considered near age appropriate ” – 34 months

> “ She talks but has a stutter. She signed her own signs for 3 years before she spoke at around the age of 4 years. She now uses 2-3 word sentences ” – 7 years

> “ He talks, his vocabulary is fairly limited but he makes himself understood. He repeats himself a lot. He started talking about 18 months to 2 years of age and now speaks in 6/7 word phrases. His speech is not always clear, some words he shortens and will not say the whole word. He also stammers sometimes like is biding time to get his words out ” – 7½ years

Behaviour

Some children with 17q12 microduplications have behavioural difficulties

Children with this microduplication are often described as happy, sociable and loving with a good sense of humour. However, some children have behavioural difficulties. One child in the medical literature and two at Unique have been described with autistic spectrum disorder (ASD). Two children have a sensory processing disorder (a range of difficulties with taking in, processing, and responding to sensory information about the environment and from within one's own body). A 5-year-old in the medical literature has unusual stereotypical movements (random writhing and flapping of arms and legs with head nodding). Two children have self-injurious behaviour, one of whom also has oppositional defiant disorder (ODD; ODD is a condition in which a child displays an ongoing pattern of uncooperative, defiant, hostile, and annoying behaviour toward people in authority) (Casselli 2010; Nagamani 2010; Brandt 2012; Bierhals 2013; Unique).

> “ He loves to play, run, make snowmen, play with Lego and loves movies (especially the Toy Story series and The Land Before Time). He is a delightful, polite and caring little boy. He's curious, sweet-natured and a total joy to be around. He has difficulty communicating his thoughts and feelings at times which results in frequent tantrums. He has also started displaying some self-injurious behaviours such as hair pulling and biting himself. When he does these behaviours, we give him the vocabulary he is looking for and then redirect his behaviour (for example, we say "it looks like you're sad. It's okay to be sad, but it's not okay to bite yourself. Let's go play with your trains now"). He has a sensory processing disorder. Body brushing and vestibular play (swinging) were helpful, so was feeding with a vibrating spoon and letting him chew on a vibrating toothbrush ” – 34 months