



Understanding Chromosome & Gene Disorders

# 16p12.2 deletions



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## 16p12.2 deletions

A 16p12.2 microdeletion is a rare genetic condition caused by a tiny missing part of one of the body's 46 chromosomes – chromosome 16. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Even a tiny piece of missing material can disrupt development, although it doesn't always do so.

## 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 X) and a long (q) arm (the bottom part of the chromosome).

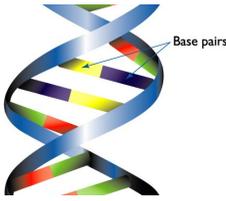
## Chromosome Deletions

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 than usual. People with a 16p12.2 deletion have one intact chromosome 16, but a piece from the short arm of the

## 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 (<http://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, referenced Unique. When this guide was written in November 2016, Unique had over 50 member families with a 16p12.2 microdeletion ranging in age from a 2-year-old to several adults.



other copy is missing. Therefore, it is believed that most of the clinical difficulties are probably caused by having only one copy (instead of the usual two) of a gene or number of genes from the missing piece. We are still learning the about the specific jobs or functions of the genes in this region. It is important to keep in mind that a child's other

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

genes, environment and unique personality also help to determine future development, needs and achievements.

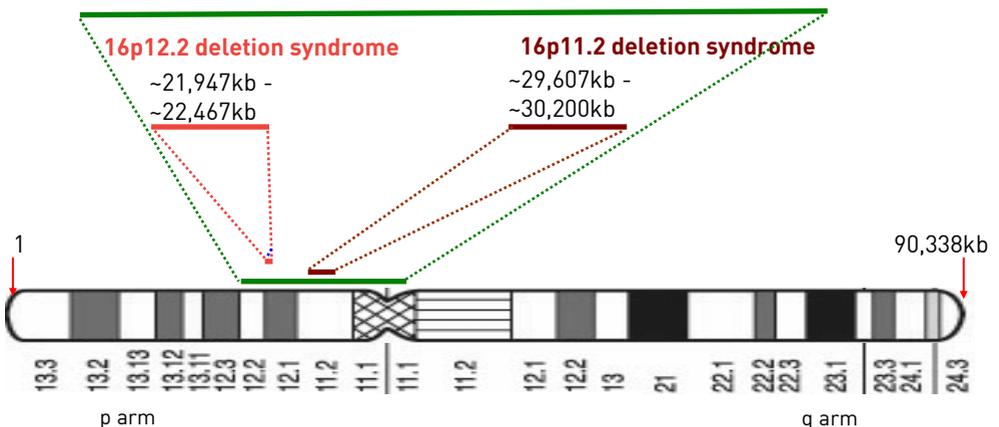
## Looking at 16p12.2

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. Looking at chromosomes in this way, it is possible to see the points where the chromosome has broken and what material is missing, if the missing piece is large enough. A missing piece visible under the microscope is called a deletion.

In the diagram at the below, you can see the chromosome bands are numbered outwards from the point where the long arm meets the short arm. In a 16p12.2 microdeletion, the chromosome has broken in two places leaving out the chromosome material between them. This particular deletion is so small that it can only be identified using molecular or DNA technology, in particular a technique using microarrays (array-CGH). This shows gains and losses of tiny amounts of DNA throughout the genome (also called duplications and deletions) and can show whether particular genes are present or not. A deletion so small that it can only be identified in this way is called a microdeletion.

### 16p11.2p12.2 deletion syndrome

~21,512kb - ~30,192kb



## Chromosome 16

The numbers in this diagram refer to the human genome build 38 (hg38; see page 5 for more details).

The deletion is around 520 thousand base pairs or 520kb, and includes 7 known genes. DNA is missing between around 21.9 Mb and 22.5 Mb, as you can see in the diagram below:

This deletion was previously known as 16p12.1 microdeletion, but as we learn more about the sequence of the chromosomes sometimes regions get reassigned. Some of the region involved that was once placed in 16p12.1 we now know is actually in 16p12.2.



## 16p11.2p12.2 microdeletion

There is a second microdeletion syndrome in this region of chromosome 16 which encompasses a larger region of the short arm, 16p11.2p12.2 microdeletion syndrome and includes the 16p12.2 region described here (see diagram on page 3). This larger deletion is described in another Unique guide: 16p proximal deletions (<http://www.rarechromo.org/information/Chromosome%2016/16p%20proximal%20deletions%20FTNW.pdf>).

Your geneticist or genetic counsellor will be able to tell you about the points where the chromosome has broken in your child. With a 16p12.2 microdeletion, the results are likely to read something like the following example:

**arr[hg38]16p12.2 (21,842,582-22,512,536)x1**

**arr** The analysis was by array (arr) comparative genomic hybridisation (cgh)

**hg38** Human Genome build 38. 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

**16p12.2** The chromosome involved is 16 and the position of the deletion is in band p12.2

**21,842,582-22,512,536**

The base pairs between 21,842,582 (around 21.8Mb) and 22,512,536 (around 22.5Mb) have been shown to be deleted. Take the first long number from the second and you get 669,954 (0.67Mb or 670kb).

This is the number of base pairs that are deleted.

**x1** means there is one copy of these base pairs, not two – one on each chromosome – as you would normally expect

## Genome Assemblies

The human genome project, an international effort to sequence the entire human genome and map all of its genes, was announced complete in 2003. However, there were many gaps in the sequence and mapping data, and scientists have since been working continuously to identify the missing information. When new sequence information is identified, the base pair numbers of each chromosome change slightly and hence the numbers for individual genes, deletions, and duplications and so on can shift. Sometimes they only shift very little; other times quite a lot.

Each new version of the genome is often referred to as an 'assembly' or a 'build'. 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 38 (GRCh38) or human genome 38 (hg38), which was released in 2014. Confusingly, you will often see the DNA sequence data for previous assemblies such as hg19 or hg18 on your/your child's genetic report, so genes and genetic changes may well have different base pair numbers. Please contact Unique or your genetic specialist for any help with understanding the report.

## Are there people with a 16p12.2 microdeletion who have developed normally and have no health, learning or behaviour difficulties?

Yes, there are. The 16p12.2 microdeletion can be 'silent'. Some of the parents of children with a 16p12.2 microdeletion have the same microdeletion but do not have any unusual features or delayed development. Other parents who also have the deletion are affected with mild learning disabilities or psychiatric diseases. Some children with a 16p12.2 microdeletion also develop normally (Girirajan 2010; Unique).

The effect of some genetic variants ranges from being barely perceptible to being obvious and severe. In this sense, they are like infections such as flu that can be mild or serious.

From a number of reports, it seems that the number of boys with the deletion who show symptoms is higher than the number of girls with the deletion who show symptoms. This raises the possibility that the deletion has a greater impact on boys than girls (Girirajan 2010).



## How much do we know?

Comparing different children and adults with a 16p12.2 microdeletion 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.

## How common is it?

The first published description of a person with a 16p12.2 was in 2007 (Ballif 2007). There have since been around 65 cases reported in the medical literature worldwide.

It has been estimated that the incidence of 16p12.2 microdeletion is about 1/15,000. However, the subtle and variable features of this microdeletion means that many people are likely to be undiagnosed (Girirajan 2010).

## Most common features

There seems to be a large variability in the clinical features of people with a 16p12.2 deletion. Additionally, every person with a 16p12.2 microdeletion is unique and so each person will have different medical and developmental concerns. No one person will have all of the features listed in this information guide, but here are some common features that have been described:

- Developmental delay
- Children are likely to need support with learning. The amount of support needed by each child will vary
- Speech and language delay
- Floppiness (hypotonia)
- Small head size
- Growth delay
- Heart problems in some

## 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.

Around a quarter of children with 16p12.2 deletion and developmental delay or intellectual disability carry an additional chromosome change (CNV), and it seems that those who do are affected more severely (Girirajan 2010; Kirov 2013; Rees 2014).

## Pregnancy and birth

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

Many mothers carrying babies with a 16p12.2 microdeletion experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth or later in childhood. As we mentioned before, clinical symptoms that come with 16p12.2 deletion are very variable, and even many mothers do not experience problems in pregnancy. Complications in mothers carrying a baby with a 16p12.2 microdeletion have also been reported. One baby had fluid on the brain on ultrasound scan. One mother's antenatal AFP blood result came back high but the ultrasound scan was normal. She also had bleeding during pregnancy and the baby was small for dates with low fetal movement. One baby in the medical literature had hypoplastic left heart syndrome (HLH; a birth defect that affects normal blood flow through the heart) diagnosed prenatally; another had a two-vessel umbilical cord. One mother had polyhydramnios (an unusually high volume of amniotic fluid). Polyhydramnios can result in premature delivery due to overdistension of the uterus) (Girirajan 2010; Unique).

## First signs and age at diagnosis

For many children, the first signs of 16p12.2 microdeletion were delays in reaching developmental milestones such as sitting and moving or speech or growth delay. Others were diagnosed due to learning or behavioural problems. The age of diagnosis varies from a baby of 6 months to adulthood (most often after the diagnosis of their child) (Girirajan 2010; Unique).

## Feeding and growth

Feeding and growth can be affected in children with 16p12.2 microdeletion

Around two fifths of the children described with 16p12.2 microdeletion had growth delay. The majority of birth weights recorded at Unique were within the normal range, with an average of 3.18kg (7lb), suggesting that for most the growth delay does not start before birth.

However, two out of 12 members of Unique had a low birth weight (below 2.6 kilos) at term. One baby was born early (before 37 weeks). One child with a 16p12.2 microdeletion had a low birth weight and length (Girirajan 2010; Rees 2014; Rai 2015; Unique).



## Range of birth weights (at or near term):

2.04 kg (4lb 8oz) to 3.94 kg (8lb 11oz)

Microcephaly (a small head) has also been described in a number of children. Two of those with a small head described by Girirajan had normal growth (Girirajan 2010).

After birth, babies tend to grow more slowly than their peers, with a small minority of babies described as growth delay". This term is used to describe a baby who has poor weight gain and physical growth failure over a period of time (Unique).

Feeding problems in babies can also be an issue. Hypotonia (low muscle tone) has been described in almost half of children carrying 16p12.1 deletion and can lead to difficulties with sucking and swallowing, and/or latching on to 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 of the end of the bed for sleeping. If these measures are not enough, feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. Some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage. A number of parents report feeding issues including difficulty biting and swallowing leading to choking. A child needed a temporary gastrostomy tube (a G-tube, feeding direct into the stomach) and one child needed a naso-gastric tube (NG-tube, passed up the nose and down the throat) as babies. Another child has a diagnosis of dysphagia (difficulty or discomfort swallowing) (Unique).

Constipation has also been reported in some children. Dietary changes and/or medication can help to manage the problem (Unique).

“ When she was an infant she had difficulty swallowing formula and would choke easily when cereal was added. When started with baby food we would have to give her small amounts. As a toddler she was not able to understand how to chew and swallow her food until almost 2½ years old. We would have to cut up food for her to make sure bite size so she could swallow without choking. The speech Therapist that treated her believed she had low muscle tone in her jaw. Right now we still have to cut her food up in bite sizes and she still uses a sippy cup. ” 3 years



“Now that he is older, he is an extremely fussy eater. He will only eat certain types of food.” 8 years

“Choking issues have always been a thing for her. Now at the age of 10, she still doesn't really care for the cold items, she can feed herself. She doesn't do that well with rice. She has a very healthy appetite and has become a lot less messy in eating on her own. Jalen suffers from chronic constipation but this is managed with two slices of double fibre wheat bread given daily.” 11 years

“He would gag on some food as a toddler and also had a tendency to overload his mouth, rather than hold finger food himself. Seemed to outgrow gagging, probably due to him avoiding certain foods himself maybe.” 13 years

## Motor skills (sitting, moving, walking)

Children with a 16p12.2 microdeletion are often delayed in learning to sit and walk.

Some children have reported motor delays, which means it may take a little longer for them to roll over, sit, crawl and walk. From the information that is available, rolling over is mastered between 4 months and 11 months (at an average of 7 months); sitting unaided is mastered between 5 months and 15 months (at an average of 11 months); crawling is



mastered between 9 months and 2 years (at an average of 14 months) and walking is mastered between 1 year 2 months and 2 years 9 months (an average of 1 year and 8 months).

One of the causes of the delay in mobility in children with a 16p12.2 microdeletion is hypotonia, which is common in those with 16p12.2 microdeletion. This makes a child or baby feel floppy to handle and generally improves and may disappear with physiotherapy and exercises (Girirajan 2010; Unique).

However, some children and adults have shown no delays in reaching their motor milestones (D'Alessandro 2014; Unique).

“Has difficulty walking down steps, if more than 2 steps she needs assistance even with rails. Sits in 'w' position. Clumsy constantly bumping



into objects. Favourite activity is dancing (spinning in circles) and singing. ” 3 years

“She loves to chase her brothers. She does not like swinging. She does stumble a lot. ” 3 years

“She has no problem walking around on even surfaces and can even run pretty well. On uneven surfaces she goes a little slower and seems unsure of herself until she gets her balance and footing down. Stairs she is able to climb up and down maybe at a slower rate but she knows to hold on and uses the rails to assist her as needed. She hates elevators [escalators] but will ride on them as she clutches to you. ” 11 years

“He has no spatial awareness and depth perception. He goes up and down stairs with both feet on the same step each time & holds rail...only now at 13 years beginning to go one on each going up our stairs, but not on unfamiliar ones. He has balance issues. Dislikes escalators and avoids them as too difficult to judge. Dislikes parks as can be a challenge and sees others his age doing what he finds hard. ” 13 years

## Fine motor skills and self care

Fine motor skills may be affected in children with a 16p12.2 microdeletion Hypotonia can also affect fine motor skills in children with a 16p12.2 microdeletion, 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 (Unique).

“She has in the past had issues transferring from hand to hand but all is better now. She has had physiotherapy and occupational and speech therapy from the age of 6 months. ” 3 years

“He has problems with holding pens/pencils so his teacher makes him use a pencil grip. He can't cut up his food properly and tends to just pick his food up and use his hands a lot. He struggles with buttons and zips, putting his

shoes/clothes on. Although he is getting better at these things. He has made progress. ” 8 years

“She is able to feed herself with very little mess these days although we still put a makeshift bib on her just in case for those messy dishes. Writing still difficult for her however we are making head way with that as well. ” 11 years

“Fine motor difficulties with holding cutlery, pencils, scissors etc. Prefers using his fingers to eat with. Classed as a clumsy child earlier on, used to try & stack bricks but ploughed them down with his force, unintentionally. Finds simple jigsaw puzzles hard to manipulate & match. Breaks things without realising how heavy handed he can be. Spills drinks & messy eater with his lack of hand eye coordination & drops things. He uses side of fingers instead of tips to pick small things up with. Throwing & catching a ball hard in primary years. ” 13 years

Toilet training may also be affected (Unique).

“It took us ages to get him to be dry during the day. He was about 5 when he was fully dry. He started reception class and was still having accidents. He has nocturnal enuresis and wets the bed most nights. We are currently seeing an incontinence nurse. ” 8 years

“He is 13 years & has some incontinence issues with daytime dribbling & wetting later during the evening when either tired or concentrating on an activity. He will sit in wet pants & not realise he is wet. In pull ups at night but showing some dry nights lately. ” 13 years

## Learning

Children with a 16p12.2 microdeletion may have learning (intellectual) disabilities

Learning in people with a 16p12.2 deletion is very variable with a full spectrum of ability. A number of parents who were diagnosed after their children were tested and also those who had genetic investigations for heart defects have no learning difficulties and include a parent with a doctorate degree (Girirajan 2010; D’Alessandro 2014; Unique). In addition, a number of children have shown no evidence of a learning disability. However, others have been described with learning disabilities ranging from mild to severe. In a study in 2014, it was found that carriers with 16p12.2 deletion exhibited lower cognition measures compared with a control population (Stefansson et al. Nature, 2014). A number of children are hyperactive or described as being easily distractible or having a poor concentration span, which can make learning more of a challenge (see Behaviour page ?). A child with a learning disability is likely to need some learning support, and many children benefit from attending a special educational school (Unique).

“Her learning is above her age level and her IQ is high. She knows her ABCs and can identify them. She knows her numbers and knows her colours. ” 3 years

“His development is behind other children his age. As he is now 8 this is becoming more and more noticeable, especially at school. He is currently in a mainstream school; however, it has now been recommended that he should attend a special school so we are currently in the process of him being assessed for this.” 8 years

“After a lot of thought, researching and discussion my husband and I decided three years ago that she would benefit from a home school setting as opposed to the public school setting where they were unable to meet her very unique needs. It was the best thing we could have done for her. She responds very well to the one on one instruction time. She is still given the opportunities to be among her typically developing peers whether in a social setting or her weekly dance classes which she enjoys very much. She has an excellent memory. She can read with assistance, someone to keep her on task and reading left to right. Visual scanning sometimes a problem for her, but she strives to pay attention and listen. We work a lot on sight words and synthetic phonics. She can write and draw although she normally will not write for long without getting frustrated which is why we incorporated typing on the computer in the mix. She can draw faces.” 11 years

“He has moderate learning difficulties. He is still behind his peers of the same age at 13 years and attends SEN [special educational needs] school. PE is his hardest subject at school and he dislikes it. Memory & sequencing difficulties (dyscalculia). Has a good sense of humour and likes ICT but finds areas involving maths very hard. Has recently gone up a group in English. Likes History but has not much scale for time.”

## Speech and communication

Speech and language delay is common in children with a 16p12.2 microdeletion

Speech and language development is another symptom highly recurrent in children carrying 16p12.2 deletion, but it is not known whether the delay was in line with the child's cognitive abilities (Girirajan 2010). One was still non-verbal at 6 years and another remained nonverbal in adolescence (Girirajan 2010). However, children with 16p12.2 deletion and normal speech development have also been reported: Those diagnosed with a 16p12.2 deletion because of investigations for heart defects did not show any delayed development in language (D'Alessandro



2014). Similarly, normal early language development was described in the report of a 1-year-old child with the microdeletion (Rai 2015).

“She has taught herself some Makaton from Mr Tumble. She uses gestures and a couple of recognisable words e.g. eat. ” 3 years

“She is verbal and is able to communicate her needs. Prior to starting play therapy at 18 months, she was not able to communicate her needs until she started sign language. ” 3 years

“He uses speech however he has a speech delay/severe communication impairment. He has improved over the years, but he still struggles with certain words and to get his point across. He can now say sentences, however he gets mixed up with words quite a lot. He tends to forget words that he needs to use. He gets sentences mixed up. Some words he says are still hard to understand, so he has to repeat himself quite a bit. We have to break our sentences down for him to understand too, for example if we asked him to do two things, he would get mixed up and not understand. ” 8 years

“We started using signs for some things at age 3; at age 10 she still relies on signs and verbal approximations for a lot of things but at this age she is able to say many words that are clear enough for even someone who doesn't know her to recognise. She can link two to three signs together when appropriate and depending on when and what she is talking about she does string her words together to make sentences. Sometimes she does speak very fast and you have to get her to repeat and slow down. Computer, iPad applications both have proven to give her the avenue to show what she knows and what she doesn't. She has been able to operate computer for quite some time. She needs no assistance mostly with these tasks, she is very good at both. ”

## Growing up with a 16p12.2 deletion:



5 years



11 years

“Spoken sentences now. Was a late unclear talker and I [mother] self referred to SALT [speech and language therapy]. Not sure when started to talk but had SALT before primary school. Still has communication difficulties now and needs time to think and knows more than he can explain/find the right words.” 13 years

“He communicates well and he likes to chat; long stories (with repetitions).” 15 years

## Behaviour

Some children with a 16p12.2 microdeletion have behavioural difficulties

Many parents describe their children as being very loving and happy. Around half of the children in one study have behavioural problems including poor attention in three, and aggressive behavior in two (Girirajan, 2010). This is a similar picture to what we see at Unique. Autistic traits or autistic spectrum disorder (ASD) have also been reported in several people with a 16p12.2 microdeletion. A diagnosis of autism can be extremely helpful in accessing services and tailoring the educational and behavioural therapy to meet the specific needs of a child with autism (Girirajan 2010; Unique).

Additionally, affected children are more likely than children without the 16p12.2 microdeletion to have attention deficit hyperactivity disorder (ADHD), which is characterised by restlessness and a short attention span (Girirajan 2010; Unique).

Later in life during adolescence and adult years, some people with a 16p12.2 deletion seem to be at an increased risk of developing mental health problems such as depression and schizophrenia (Itsara 2009; Girirajan 2010; Kirov 2014; Rees 2014). Schizophrenia is a mental health condition that causes a range of different psychological symptoms, including hallucinations (hearing or seeing things that do not exist) and delusions (believing in things that are untrue). Schizophrenia can be treated using a combination of medical treatments such as antipsychotic medicines, and psychological interventions such as cognitive behavioural therapy.

“She loves playing with her sisters, painting and drawing, dancing, singing - she makes up her own songs (in her own language). She loves her dog Miffy. She is very loving and a joy to be around.” 3 years

“She is obsessed with horses both real and toy horses. When we can we take her riding. Loves to sing and dance sometimes makes up her own songs. She likes videos of dancing or singing. She will become obsessed with one particular artist and watch it over and over. Loves watching videos of horses. She prefers to play alone and will play with others but in the end prefers to be alone. She has mood swings up and down and there is no consoling her when she is upset and a lot of the time we never can figure out what is wrong. She is currently scheduled to see a behaviourist. Repetitive

behaviour –spinning a lot during the day. ” 3 years

“She is a very healthy, strong, loving child. When she decides she wants to do something she is stubborn as a mule. She is very caring and loving and can sense when others around her are down or in need of some hugs and kisses or just cheering up. Loves playing with her brothers, the Xbox, Lego games, watching TV shows. She does really well with the computer. Has fun playing with mom and family as well. She acts shy in new social situations. Sometimes she can be extremely loud. She is as stubborn as they come so when you tell her no and she wants to do something she may bite her foot, pull her hair, call you mean, point at you and spit. All these behaviours can be challenging however she is pretty easy to calm down once you help her talk through it and go from there. She is the first to say she is sorry. ” 11 years

“Is quiet around other people until he gets to know you, if you have a sense of humour he will like you and can tease you. If he finds you less funny, he will think you moody (mis-reads the situation). He will not be rushed and will tell you accordingly (had detention from school because of this attitude). He can be the most funny, loveable little boy, but can easily turn to anger if he mis-reads a situation ” 13 years

“He is social, generous (and naive). But he cannot always control his emotions and frustrations, especially when he is tired. He is aware of his limits and he wonders why he is different and he even asked the paediatrician about a possible treatment. He wants to have friends and a nice “normal” girlfriend (this is major concern at age 15); for the future he would like to be independent (with some supervision) and have a wife. ” 15 years

## Sleep

Sleep problems seem to be more common in children with a 16p12.2 microdeletion, and some children take melatonin to help them to regulate their sleep (Girirajan 2010; Unique).

“She sleeps at unusual times and she prefers to sleep in the day. ” 3 years

“She always has trouble going to sleep and staying asleep. She is on melatonin. ” 3 years

“She has issues with both going to sleep and staying asleep. She is currently on medication as she was barely getting 6 hours of sleep at night and stopped taking naps. ” 3 years

“Everything has to be in its right place & turned off before he can settle to sleep. He dislikes (almost afraid) of going to sleep. Noises awaken him or he occasionally sleep walks or even sits up in his bed and talks/mumbles in his sleep. Sleeps with a small soft teddy. ” 13 years

## Facial appearance

Children with 16p12.2 microdeletion may have a subtle characteristic facial appearance.

Geneticists trained to note unusual features may find in those with a 16p12.2 microdeletion features as a flat face, downslanting eyes and unusual shaped or positioned ears, but there is no consistent pattern among those with the microdeletion (Girirajan 2010; Unique).

## Hands and feet

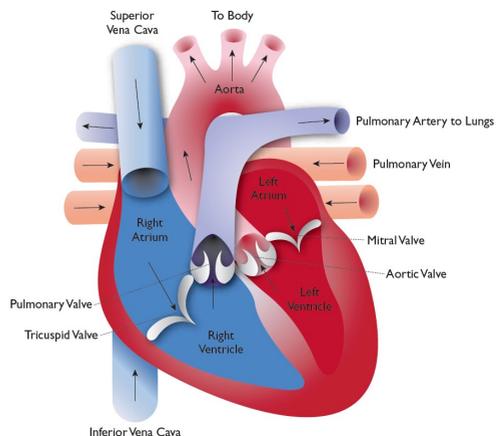
Hand and foot anomalies appear to be common in those with 16p12.2 microdeletions and include long tapering fingers, small hands with short fingers, polydactyly (extra fingers); incurving little fingers (5th finger clinodactyly); flat feet, minor syndactyly (two or more fingers or toes are fused together) and overlapping toes. Overall, the pattern is of variable minor hand and feet anomalies (Girirajan 2010; Rees 2014; Unique).

## Health matters

### ■ Heart

Cardiac problems have been reported in several people, and having a 16p12.2 microdeletion may be a risk factor for heart problems. In the study of Girirajan and colleagues, 7/21 people had congenital heart disease. Two had hypoplastic left heart syndrome (HLHS, the left side of the heart has not

developed properly and is very small. The aorta, the artery that carries blood from the heart around the body, is tiny and blood can only reach it through the ductus arteriosus, a blood vessel that normally closes within days of birth); one had a bicuspid aortic valve (BAV, a congenital defect in the aortic valve where the valve has only two cusps (flaps) rather than the usual three. The aortic valve ensures that the blood flows only in one direction. When the valve is bicuspid there can be a tendency for the valve to leak). Two have been described with a ventricular septal defect (VSD; a hole in the wall between the two pumping chambers of the heart, the ventricles) (Girirajan 2010; Unique). One person had Tetralogy of Fallot (TOF, the artery that takes the blood to the lungs has an unusually narrow entrance (pulmonary stenosis), and there is also a VSD) (D'Alessandro 2014). One had pulmonary stenosis (a narrowing of the pulmonary valve, meaning that the heart has to work harder to pump blood which results in breathlessness) (Unique).



In addition, a large study looking for genetic changes in people with congenital heart defects identified three people with 16p12.2 microdeletions (Geng 2014).

## ■ Seizures

Children with a deletion at 16p12.2 may have an increased risk of seizures

Many children reported in the medical literature and at Unique have experienced seizures and /or had abnormal results on (EEG), although seizure types and severity vary widely. Seizures are frequently controlled with anti-epileptic medications (Girirajan 2010; Unique).

## ■ Spine

Several people have been described with spinal problems including a tethered spinal cord (the spinal cord is abnormally attached to the tissues around the spine) and scoliosis (curvature of the spine) (Girirajan 2010; D’Alessandro 2014; Rai 2015; Unique).

## ■ Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers, so regular and high quality dental care is important (Unique).

## ■ Genital anomalies

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. These include undescended testes (which can be brought down surgically), hypospadias (the hole usually sited at the end of the penis is on the underside instead), chordee (the head of the penis curves downward or upward) and congenital scrotalised penis (in which the penis appears to arise from the scrotum instead of the abdominal wall) (Girirajan 2010; de Jong 2010; Unique).

## ■ Eyesight

A number of children have been reported to have a squint (strabismus), where one or both eyes can turn inwards, outwards or upwards. Many squints are convergent (the eyes cross) and many children need surgery to re-align the eyes. A few people have astigmatism, which is when the cornea (the clear cover over the iris and pupil) is abnormally curved. The effect on vision is to make objects appear blurred. Sometimes the brain can compensate for astigmatism, although it may be too strong for this to happen without glasses. Several people have been reported to have long or short sight. One person is reported to have amblyopia (a lazy eye. For many possible reasons, the brain prefers one eye, reducing the vision in the other eye). One person has peripheral vision loss (Girirajan 2010; Unique).

## ■ Hearing

Generally speaking, children have had normal hearing, although young children sometimes have the fluctuating temporary hearing loss caused by a build-up of fluid behind the eardrum (glue ear) but they outgrow this naturally. If it is severe

or persistent tubes (grommets) may be inserted into the eardrum to aerate the space (the middle ear) behind it and improve hearing (Unique). In the published medical literature hearing loss has been described in three people (Girirajan 2010).

### ■ Other

Other health concerns which may or may not be linked with the microdeletion (because they have only been reported in one or a few people) include renal abnormalities [small kidneys, horseshoe kidney (the two kidneys are fused together to form a 'horseshoe' shape) or hydronephrosis (a condition in which one or both of the kidneys become stretched, or swollen, due to a build-up of pressure when urine fails to drain out of the kidney)]; two had a cleft palate (a split, 'cleft', in the soft part of the palate); two had clubfoot or bowed legs; craniosynostosis (a rare skull problem that causes a baby to be born with, or develop, an abnormally shaped head because the plates of the skull fused too early.); inguinal hernia (tissue from the intestine forms a swelling or a bulge in the groin) and tracheal agenesis (the windpipe is absent) (de Jong 2010; Girirajan 2010; D'Alessandro 2014; Rai 2015; Unique).

## Treatment for 16p12.2 microdeletions

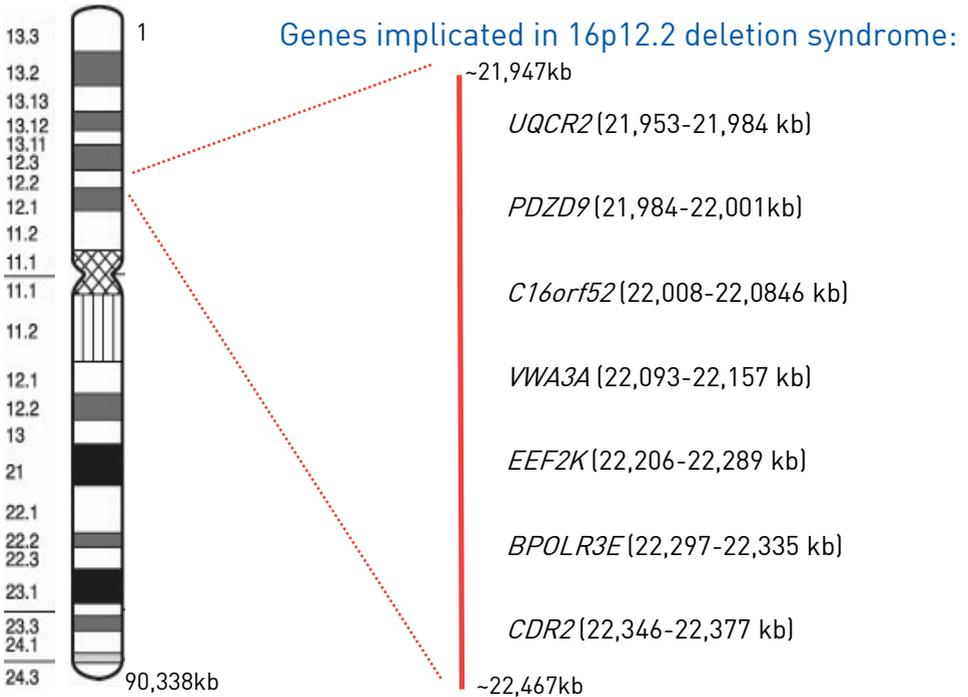
Because the features of this microdeletion are so variable, treatment is targeted at the specific problems identified. Early diagnosis and management result in the best outcome. Referral to appropriate medical specialists may be necessary and may include a developmental/behavioural paediatrician, paediatric neurologist and a clinical geneticist.

## Some genes in 16p12.2

Most deletion and duplication disorders are the result of non-allelic homologous recombination (NAHR) between large (more than 10kb) and highly similar sequences called segmental duplications. Several chromosomes are enriched in these types of DNA sequences, such as chromosome 16 and especially the short arm. This means that there is a higher frequency of deletions and duplications in this region.

The common microdeletion at 16p12.2 is 520kb and includes 7 genes: UQCRC2, PDZD9, C16orf52, VWA3A, EEF2K, POLR3E, and CDR2. At the moment, we do not know enough about any of these genes to say why having only one copy of each of these genes results in the features of a 16p12.2 microdeletion.

A large study looking for genetic changes involved in congenital heart disease identified three patients who had heart disease and also had a 480kb deletion involving EEF2K and CDR2 genes, suggesting that these two genes might be potential risk factors for heart problems (Geng 2014).



It is important to remember that while identifying the gene(s) responsible for certain features of the 16p12.2 microdeletion 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 missing, 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.

## Why are people with a microdeletion in this region so different from each other?

One reason for the differences is that the amount of missing chromosome material and number of missing genes is larger in some people. But people in the same family with the same size microdeletion can be differently affected. We don't yet understand all the reasons for this but one possible explanation is what is called the 'two-hit' model. This model explains that 16p12.2 deletion predisposes an individual to develop some type of neurodevelopmental disease, and the identity of the final clinical outcome will be the consequence of this deletion in presence of other genetic variants (Girirajan 2010).

## Adults

Unique has several adults who are unaffected by the 16p12.2 microdeletion, and only discovered they carried it after their child was diagnosed. In the study by Girirajan and colleagues, 13 parents were assessed. Some were unaffected by carrying the microdeletion. However, parents who had the microdeletion were more likely than those without to have a learning disability than those who did not have the microdeletion. Carrier parents were more likely than non-carrier parents to be affected by a learning disability, depression or bipolar disorder, or seizures (Girirajan 2010).

Genome-wide association studies are a relatively new way for scientists to identify genes involved in human disease. This method searches the genome for small variations such as microdeletions, that occur more frequently in people with a particular disease than in people without the disease. Such studies have been done to try to discover if there is a genetic link to developing schizophrenia and one such study identified 13 people with schizophrenia who also have a 16p12.2 deletion. The study also picked up 6 people from the control population (those without schizophrenia) who had a 16p12.2 deletion. This study and other studies have suggested that a number of rare genomic rearrangements, such as microdeletions and microduplications, have been shown to increase the risk of developing schizophrenia. It is important to remember that the involvement of a 16p12.2 microdeletion in schizophrenia is just a risk factor and it is likely to be one of many risk factors involved in the development of schizophrenia - a 16p12.2 microdeletion alone is unlikely to be sufficient to cause schizophrenia (Girirajan 2010; Rees 2014).

## In your family, is the 16p12.2 microdeletion inherited or not?

16p12.2 microdeletions can occur out of the blue for no obvious reason, or they can be inherited from either parent. Studies so far suggest that most are inherited from one of the parents (Girirajan 2010). The only way to be certain is to check the chromosomes of both parents, even if they are themselves completely healthy. If one parent has the same microdeletion, we can assume that it has been passed on.

If both parents have normal chromosomes, the 16p12.2 microdeletion is in all likelihood a new occurrence. The genetic term for this is *de novo* (dn). A new 16p12.2 microdeletion has been caused by a mistake that occurred either when the parents' sperm or egg cells were formed or in the very earliest days after fertilisation.



As a parent, there is certainly nothing you could have done to prevent this from happening. No environmental, dietary, workplace or lifestyle factors are known to cause 16p12.2 microdeletions. There is nothing that either parent did before or during pregnancy that caused the microdeletion – so no one is to blame and there is no reason for anyone to feel guilty.

## **If one person in a family with the microdeletion 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. We know that if one person is mildly affected, others may be more severely and obviously affected. There are many descriptions of unaffected parents only discovering they carry a microdeletion after it has been detected in their affected children (Girirajan 2010; Pizzo, EJHG, 2016).

## **Can it happen again?**

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 16p12.2 microdeletion 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 16p12.2 microdeletion. 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 deletion.

In families where the 16p12.2 microdeletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 16p12.2 microdeletion rises to 50% in each pregnancy. However, the effect of the microdeletion on the child's development, health and behaviour cannot be reliably predicted and some individuals can even carry the deletion with no obvious effect.

Your genetics centre should be able to offer counselling before you have another pregnancy.

## Will my child with a microdeletion have similarly affected children?

Your child with a microdeletion may well want to have children. We have not known about the condition for long enough to be certain if it affects fertility, but it is likely that fertility will be normal. In each pregnancy, someone with the deletion has a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the deletion. Their ability to look after a child is very likely to be closely related to their own learning ability.

Although the risk of passing the microdeletion on to their child is 50 per cent, the risk of the child being affected by the microdeletion is lower than 50 per cent, because of the variable effect of the microdeletion and that not all people who carry it are affected.

### Families say.....

“She constantly amazes and surprises me. I am very proud of her and her accomplishments. She has taught me new ways to view the world because competition is not so very important to her. She does things because she wants to. It’s genuine and true and it’s a breath of fresh air.”

“He has taught me to use the computer. He will say he loves me (more at bed time or when he’s done something wrong). He has made me laugh with his sense of humour & with his literalness within certain situations...can be good company (until recently & change of behaviour & hiding in his bedroom). He will ‘make light’ of his misfortunes/disabilities e.g. ‘I must have everyone else’s’ spare parts’ & ‘If I have a chromosome missing, can I have someone’s who’s got one extra, that will put me right (laughing)?’ Having him has got me socialising more.”

“He is an inspiration for my work and daily life; thanks to him I never forget what’s important in life; he is supportive and lovely.”

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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 Santhosh Girirajan, Department of Biochemistry and Molecular Biology, Pennsylvania State University. USA

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