

# 22q12 and 22q13 duplications



## Duplications of 22q12 and 22q13

A duplication of 22q12 and/or 22q13 is a very rare genetic condition in which the cells of the body have a small but variable amount of extra genetic material from one of the body's 46 chromosomes – chromosome 22. For healthy development, chromosomes should contain just the right amount of genetic material (DNA) – not too much and not too little. Like most other chromosome disorders, having an extra part of chromosome 22 may increase the risk of birth defects, developmental delay and intellectual disability. However, there is individual variation.

## Background on Chromosomes

Chromosomes are structures which contain our DNA and are found in almost every cell of the body. 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 member of each chromosome pair being inherited from each parent. Most cells of the human body have a total of 46 (23 pairs of) chromosomes. The egg and the sperm cells, however have 23 unpaired chromosomes, so that when the egg and sperm join together at conception, the chromosomes pair up and the number is restored to 46. 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. Chromosome 22 is our second smallest chromosome containing between 500 and 800 genes (of the estimated 20,000 to 25,000 total genes in each of our cells).

Each chromosome has a short arm (on the left in the diagram opposite) called **p** from *petit*, the French word for small, and a long arm called **q**.

People with a 22q12 and/or 22q13 duplication have one intact chromosome 22, but their second chromosome 22 has an extra piece of the long arm. Although the exact numbers and types of genes that are included in the duplication are often not known, the extra copies of some genes usually have an effect on a person's learning and physical development. Therefore it is believed that most of the clinical difficulties are caused by having three copies (instead of the usual two) of a number of genes. We are still learning about the specific jobs or functions of the genes in these regions. Also, it is important to keep in mind that a child's other genes, environment and unique personality help to determine future development, needs and achievements.

## Sources and references

The information in this briefing is drawn from what is known about those with a duplication or microduplication at 22q. 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](http://www.ncbi.nlm.nih.gov/pubmed)). If you wish, you can obtain articles from *Unique*. The briefing also draws on *Unique's* database. In 2010, *Unique* has six members with a duplication at 22q12/13 ranging in age from 18 months to 23 years.

## Looking at chromosome 22q

### Chromosome analysis

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 the extra material is, if the extra piece is large enough. An extra piece of chromosome is called a **duplication**.

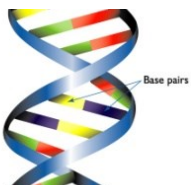
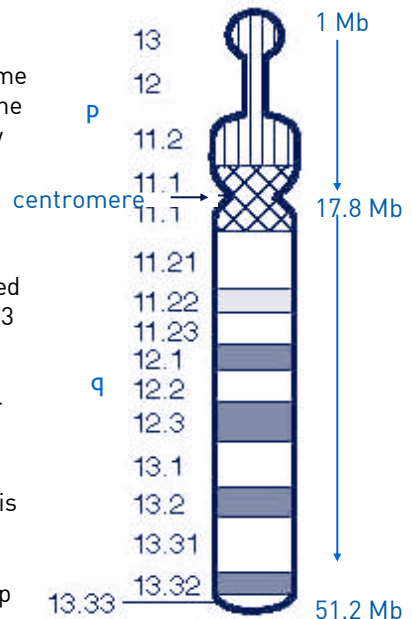
The majority of 22q12 and 22q13 duplications are **terminal**. This means that the tip of the long arm of chromosome 22 is included in the duplication. However, some duplications are **interstitial**. This is where a piece of the long arm of chromosome 22 is duplicated, but the tip (and possibly more than just the tip) is not.

In the diagram on the right you can see the chromosome bands are numbered outwards from the point where the long arm meets the short arm (the **centromere**). A low number, as in q11 in the long arm, is close to the centromere. Regions closer to the centromere of the chromosome are called **proximal**. A higher number, as in q13, is closer to the end of the chromosome. Regions closer to the end of the chromosome are called **distal**. Duplications involving bands 22q12 and/or 22q13 are therefore known as distal duplications. The duplications considered in this information guide are made up of extra material from bands 22q12, 22q13 or both, so hereafter will be referred collectively as **22q12/13 duplications**.

The extra piece can be large or it can be so tiny that it is not found using a conventional chromosome analysis. Indeed, there are at least two people described in the medical literature whose duplication was not picked up with routine karyotyping (Okamoto 2007; Pramparo 2008).

These very small duplications are called **microduplications** and can only be identified using molecular or DNA technology, in particular a technique using microarrays, that shows gains and losses of tiny amounts of DNA throughout the chromosomes. Microarrays can also show whether particular genes are duplicated or not. The break points in chromosome 22 vary from person to person, so each person will have a

different number of genes duplicated. The smallest duplications are counted in '**base pairs**'. These are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure (see diagram on the left). There are so many base pairs in chromosomes that they are usually counted in thousands or '**kilobases**' (kilo=1,000), shortened to kb; or base pairs are counted in millions or '**megabases**' (mega=1,000,000), shortened to Mb. The image of chromosome 22 above shows that it contains about 51 million base pairs (51 Mb).



*Base pairs in the twisting*

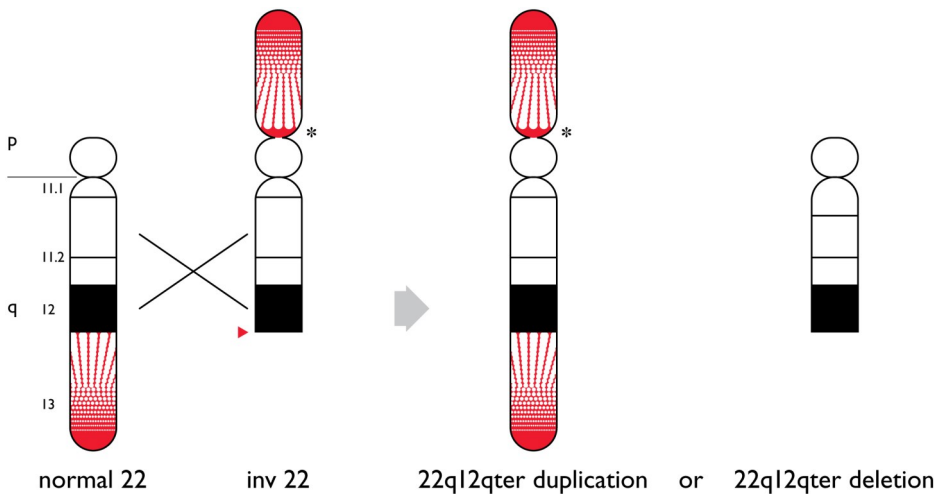
# Karyotype

If your child's chromosomes are stained, magnified and examined under a microscope and a duplication is identified, the laboratory will send a report including a karyotype. A karyotype is a way of describing what the chromosomes look like. It is likely to read something like this:

## 46,XY,dup(22)(q13.1)dn

- 46 The number of chromosomes in your child's cells
- XY The two sex chromosomes: XY for males; XX for females
- dup A duplication, or there is extra material
- (22) The duplication is from chromosome 22
- (q13.1) The chromosome has one breakpoint, in band 22q13.1. The material from this point until the end of the chromosome is duplicated
- dn dn is a short way of writing *de novo*. This means that both parents' chromosomes have been checked and nothing unusual found at 22q13. The duplication has occurred for the first time in this family in this child and is not an inherited rearrangement.

Some 22q12/13 duplications are inherited from a parent who has what is known as an inversion. An inversion of chromosome 22 occurs when there has been a break in the long arm of chromosome 22 (see diagram below) and the broken off segment turns through 180° and attaches itself to the short arm of chromosome 22. Usually, inversions do not affect the health or development of the person with the inversion but there is a risk of producing sperm or eggs with an unbalanced chromosome 22 (either a deletion or a duplication, see diagram below) (Boyd 2005; Hou 2005).



The bottom of the q arm has broken off (at ►), rotated 180 degrees and attached to the p arm (at \*). Someone carrying this inversion is unaffected since no material has been lost or gained.

In these cases the report may read something like this:

### 46,XY,rec(22) dup(22)(p13q13.1)mat

46	The number of chromosomes in your child's cells
XY	The two sex chromosomes: XY for males; XX for females
rec(22)	One of the copies of chromosome 22 is a <b>recombinant</b> (a chromosome that has extra, or missing material)
dup(22)	A duplication, or there is extra material from chromosome 22
inv(22)	There is an inversion on chromosome 22
(p13q13.1)	The chromosome has a break point, in band 22q13.1. The material from this point until the end of the chromosome is duplicated and is attached to the short arm of chromosome 22 at band p13
mat	The duplication has been inherited from the mother; <b>pat</b> would indicate that the duplication was inherited from the father

## Array CGH report

You may be given a molecular report, which may read something like this:

### arr[hg19] 22q13.1q13.2 (36192000-43378000)x3

arr	The analysis used microarray technology
hg19	Human Genome build 19. This is the reference DNA sequence that the 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
base	

22q13.1q13.2 The analysis revealed a duplication from band 22q13.1 to 22q13.2 (36192000-43378000)x3

Three copies of the piece of the chromosome between base pair 36192000 (in 22q13.1) and base pair 43378000 (in 22q13.2) were found instead of the expected two copies. The first number is the start of the duplication and the second is the end of the duplication. The difference between them is the number of extra base pairs, 7156000 (7.156 Mb)

Comparing your child's karyotype with others, both in the medical literature and within *Unique*, may help you build up a general picture of what to expect. But there will still be differences between your child and others with apparently similar karyotypes. Every child is an individual.

## How common are 22q12 and 22q13 duplications?

Duplications of the proximal region of 22q are not uncommon, especially duplications due to familial (11;22) translocations (*Unique* has a separate information guide on this, 11;22 Translocation) and Cat-eye syndrome (inversion duplication 22q) and 22q11.2 microduplications have been described recently in a number of people. However, pure duplications of 22q12/13 are have been rarely detected and only around 25 people have been reported in the published medical literature. Deletions of the same region of 22q13 have been reported much more frequently and give rise to Phelan-McDermid syndrome (*Unique* has an information guide on this syndrome, 22q13 deletions). However, a deletion of a chromosome is much easier to see under the microscope than a duplication, so until array CGH is more widely used the number of people

diagnosed with deletions will be greater than the number of those diagnosed with duplications. However, we now know that the frequency of the duplication and the frequency of the deletion should be about equal and we expect that more individuals with a duplication of 22q13 will be diagnosed as the array CGH test becomes more widely available.

## Duplications seen at *Unique* and in the medical literature

The number of individuals affected by each duplication is shown in brackets

Duplication of 22q12 and 22q13	Duplications of 22q13	Interstitial duplications
22q12qter (8) (Cantu 1981; Jensen 1984; Rivera 1988; Abeliovich 1989; Johnson 1990; Barajas-barajas 2004)	22q13qter (3) (Fryns 1980; Petek 1990; <i>Unique</i> )	22q11.2q13.1 (1) (Prasher 1995)
22q12qter (1) ( <i>Unique</i> )	22q13.1 (3) (Aleck 1999; Boyd 2005; Hou 2005)	22q12.1q13.1 (1) (Gentile 2004)
22q12qter (1) (Tonk 2004)	22q13.2qter (3) (Schinzel 1981; Biesecker 1995; Feenstra 2006)	22q13.1q13.2 (1) (Pramparo 2008)
	22q13.3qter (4) (Wieczorek 1998; Feenstra 2006; <i>Unique</i> )	22q13.1q13.31 (1) (Shimajima 2009)
	22q13.31 (1) ( <i>Unique</i> )	22q13.31q13.3 (2) (Okamoto 2007; <i>Unique</i> )
		22q13.2q13.3 (1) ( <i>Unique</i> )

## Most common features of a duplication of 22q12/13

Every person with a 22q12/13 duplication 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 guide. However a number of common features have emerged:

- Learning (intellectual) difficulties
- Growth retardation, both in the womb and after birth
- Failure to thrive
- Motor delay
- Floppiness or hypotonia
- Microcephaly
- Unusual facial features
- Minor genital anomalies in boys

## What is the outlook?

The outlook for any baby or child depends on what segment of chromosome 22q has been duplicated and how this has disrupted early development in the womb. Since most of those who are known to have a 22q12/13 duplication are children, long term follow-up is necessary. However, it has been suggested that those with more proximal

duplications (involving bands 22q12 and 22q13.1) are more severely affected than those with more distal duplications involving the bands 22q13.2 and 22q13.3.

## Pregnancy and birth

Many mothers carrying babies with 22q12/13 duplications experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, two babies were described as having intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed, resulting in babies that are smaller than expected for the number of weeks of pregnancy (Hou 2005; Shimojima 2009, *Unique*).

One baby with a 22q13.3 duplication needed resuscitating at birth and in the hours following her birth had periods of gasping for breath and spent the next five weeks in hospital (*Unique*).

## Newborn

Babies with a 22q12/13 duplication are often, but not always, small and underweight at birth with an average birth weight of 2.94 kg (6lb 8oz). The range of birth weights is between 1.3 kg (2lb 14oz) and 4.48 kg (9lb 14oz). However, half (5/10) had a low birth weight (below 2.6 kilos or 5lb 12oz). Typically babies with a duplication of 22q12/3 are floppy (hypotonic) in the newborn period. This can result in delay reaching the baby developmental milestones (such as sitting, rolling, crawling and walking) and also cause feeding problems.

## Feeding and Growth

For those with a duplication of 22q12/13, feeding difficulties are a major area of concern for families, particularly as babies usually start out small and underweight. After birth, babies tend to grow more slowly than their peers, with a small minority of babies described as 'failure to thrive'. This term is used to describe a baby who has poor weight gain and physical growth failure over a period of time. The hypotonia that is common in babies with a 22q12/13 duplication can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft or high palate can also find the action of sucking and swallowing difficult. Three babies had a gastrostomy tube (a G-tube, feeding direct into the stomach) in order to meet their nutritional needs. One of these babies began taking a bottle during the day and using the G-tube at night. At 11 months the G-tube was removed and at her first birthday party she was able to enjoy birthday cake (Wieczorek 1998; Feenstra 2006; *Unique*).

The hypotonia can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage) and can lead to aspiration pneumonia. Reflux 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. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (*Unique*).

Hypotonia also affects chewing so some children are late in weaning and need their food cutting up small or processed for a long time (*Unique*).

Around half of babies with a duplication of 22q12/13 are small at birth, with a head measurement that is smaller than expected (microcephaly). After birth their growth rate may be slower than their peers and this may be made worse in some cases by feeding difficulties. As a result many children and adults with a 22q12/13 duplication are small and light for their age (Fryns 1980; Cantu 1981; Biesecker 1995; Rivera 1998; Johnson 1990; Barajas-barajas 2004; Feenstra 2006; Okamoto 2007; Pramparo 2008; Shimojima 2009; *Unique*).

## Appearance

You and the doctors may notice that your baby has slightly unusual facial features. He or she may bear a resemblance to other babies and children with a 22q12/13 duplication. Some babies have a small head with a short neck. They often have a prominent forehead, a wide nasal bridge and low set ears. They may have widely spaced eyes (hypertelorism) with an epicanthic fold (an extra fold of skin covering the inner corner of the eye) (Fryns 1980; Cantu 1981; Biesecker 1995; Rivera 1998; Johnson 1990; Barajas-barajas 2004; Feenstra 2006; Okamoto 2007; Pramparo 2008; Shimojima 2009; *Unique*).

## Learning

Learning difficulties and intellectual disabilities are common in children with a 22q12/13 duplication. There is individual variation and it seems that children with very small terminal duplications or small interstitial duplications may have mild or moderate learning difficulties. One child with a 22q13.3qter duplication has been assessed as having only a borderline learning difficulty. However, children with larger duplications are more likely to have severe learning difficulties and will need more support with learning, and the amount of support they need may be quite considerable. They will need support and benefit from early intervention programmes and may thrive best in a special learning environment.

“ She has a good memory and loves colouring in pictures - 4 years

“ He has severe learning difficulties and cannot write or draw. He has an OK memory - 23 years

## Communication and Speech

As with learning there is a great deal of variability depending on the region of 22q12/13 that is duplicated, but speech is delayed in many children and a few do not master language and continue to use gestures, facial expressions and vocal noises to indicate their needs and express their feelings. Speech therapy has proved extremely beneficial to many children and some children use sign language and/or PECs (picture exchange communication system) help to communicate their needs and wants.

A 2½-year-old with a 22q13.2q13.3 duplication began using words at 14 months and now has 3 or 4 word sentences. A 2½-year-old with a 22q13.31qter duplication has around 50 words but is not yet putting two words together. She is able to follow one-step directions with ease and seems to understand most of what is said to her. She uses some signs but now it is mostly words. A 3-year-old with a 22q13.3qter duplication uses signing. She also speaks clearly and can use two word phrases, sometimes three.

A 4-year-old with a 22q13.1q13.3 duplication uses several meaningful words and understands simple sentences. A 4-year-old with a 22q13.1qter duplication has a few words. A 5-year-old has no speech or signs but she recognizes her parents and smiles at other children. A 4-year-old and his 40-year-old father both with a 22q13.3qter duplication have no speech problems. A 10-year-old has speech that is severely impaired and can only express a few words. A 12-year-old with a 22q13.1q13.31 interstitial duplication babbled at 2 years and spoke in sentences at 4 years. A 12-year-old has no speech or signing. He will take you where he wants to go to show you something.

A 19-year-old with an interstitial duplication of 22q12.1q13.1 has good speech.

A 27-year-old with a 22q11.2q13.1 interstitial duplication has no language and limited communication (Prasher 1995; Gentile 2004; Boyd 2005; Feenstra 2006; Okamoto 2007; Pramparo 2008; Shimojima 2009; *Unique*).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which in addition to insufficient sucking, can also affect the development of speech. Those with a cleft or high palate may also have specific difficulty with certain sounds (*Unique*).

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

Children with 22q12/13 duplications are typically slow to reach their developmental motor milestones. The evidence at *Unique* and in the medical literature is that babies sit unaided between 7 months and 4½ years (average 23 months) and crawl between 13 months and 2 years (average 17 months). Independent walking was mastered between 13 months and 6 years (average 2 years and 3 months) (Boyd 2005; Feenstra 2006; Okamoto 2007; Pramparo 2008; Shimojima 2009; *Unique*).

There are several reasons for these motor delays including the hypotonia that affects many children with a 22q12/13 duplication. Hypotonia often improves as children mature; nonetheless, early physiotherapy and occupational therapy can be beneficial.

One child has a slightly crouched gait and arms that do not fully extend; another child has a wide gait (*Unique*).



3 years

## Development: hand-eye co-ordination and dexterity (fine motor skills) and self care

Hypotonia can also affect fine motor skills in children with a 22q12/13 duplication and they may experience delay in learning to use their hands. The extent of the delay varies considerably between individuals with some children (generally those with smaller duplications) not affected at all. Others may take longer to reach for and grab toys and hold a bottle or cup. Children may experience delays in being able to self-feed and hold a pen to write or draw. Special chunky cutlery and cups with handles can be helpful. Many children have occupational therapy in order to help improve these skills although some children remain clumsy (*Unique*).

Personal care skills generally go hand in hand with the ability to grasp, hold onto and manipulate objects and toys and again there is variation with some children able to dress themselves and brush their own teeth while others depend on their family and carers. Toilet training is also delayed and may not be achievable. We only have information for three children, one who achieved daytime bladder and bowel control by the age of 3½ years; another at 9½ years and a third achieved bowel control at 10 years (Gentile 2004; *Unique*).

“She needs help getting dressed but can undress, comb her hair and brush her teeth. She is potty trained with few accidents—4 years

## Cleft palate or lip

In the medical literature a cleft palate (an opening in the roof of the mouth resulting from the palate not forming correctly during development) is reported in around a third (9/27) of babies. Two further babies were born with a high arched palate.

Two *Unique* children have a high arched palate but none has a cleft palate (Cantu 1981; Schinzel 1981; Jensen 1984; Rivera 1988; Abeliovich 1989; Biesecker 1995; Wieczorek 1998; Hou 2005; Feenstra 2006; Gentile 2004; Okamoto 2007 *Unique*).

## Heart defects

Various structural problems of the heart have been seen. The most common type of problem is a hole in the heart. The two types of holes are:

**Atrial septal defects (ASDs)** – holes in the muscular wall between the two filling parts of the heart. Some blood flows through from the left to the right side, increasing **the amount of blood flowing to the lungs. Treatment depends on the type of defect**, whether it closes spontaneously and its size. Treatment can include medical management, taking medications to help the heart to work better, control of potential infection to the inner surfaces of the heart and surgical repair with stitches or a special patch.

**Ventricular septal defect (VSDs)** – holes in the wall between the two pumping chamber of the heart (ventricles). This allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Treatment is determined individually. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from extra blood flow (Cantu 1981; Rivera 1988; Johnson 1990; Barajas-barajas 2004; Tonk 2004; Boyd 2005; Hou 2005; *Unique*).

## Minor genital anomalies

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. Cryptorchidism (undescended testes) has been noted in boys with a duplication of 22q12/13. Treatment for undescended testicles depends on the suspected cause but whatever it is, treatment is usually needed if the testicles do not descend naturally in time. If a hormone problem is suspected to be the cause, a short course of hormone treatment may be suggested. Otherwise, or if hormone treatment does not work, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy. Hypospadias (where the hole usually sited at the end of the penis is on the underside instead) has also been reported. One boy had a small penis and small testes (Fryns 1980; Cantu 1981; Fujimoto 1983; Rivera 1988; Petek 1990; Prasher 1995; Hou 2005; *Unique*).

Genital anomalies have also been reported to affect girls. Two girls have hypoplastic (underdeveloped) labia and one has ovarian dysgenesis (inactive ovaries) (Cantu 1981; Boyd 2005).

## Kidney

Two babies in the published medical literature were born with an ectopic kidney (where the kidney is located in an abnormal position). One *Unique* member had one kidney removed because it was covered in kidney cysts (Petek 1990; Feenstra 2006; *Unique*).

## Brain anomalies

Two girls in the medical literature had brain imaging that showed agenesis of the corpus callosum (ACC). The corpus callosum is the largest connective pathway in the brain.

It is made up of more than 200 million nerve fibres that connect the left and right sides (hemispheres) of the brain. ACC is a birth defect in which the corpus callosum is partially or completely absent, resulting in poorly connected or disconnected brain hemispheres. Each hemisphere of the brain is specialised to control movement and feeling in the opposite half of the body, and each hemisphere specialises in processing certain types of information (such as language or spatial patterns). Thus, to co-ordinate movement or to think about complex information, the hemispheres must communicate with each other. The corpus callosum is the main, although not the only, connector that allows that communication. The effects of ACC can be highly variable and in some children the ACC appears to have little obvious effect while others are more seriously affected (Biessacker 1995; Pramparo 2008).

Three *Unique* children have had brain imaging that showed no anomalies (*Unique*).

## Eyesight

A squint (strabismus), where one or both eyes can turn inwards, outwards or upwards due to weakness of the muscles that control the eye, is the most common vision problem. Treatment of strabismus depends on the cause but can include patching the stronger eye, exercises, glasses to correct a refractive error such as long sight and surgery to realign the muscles that hold the eye in place.

A number of other vision problems have been reported to affect just one child.



22 years

One child in the published medical literature had poor vision in both eyes and coloboma, a developmental defect in part of the structure of the eye, usually caused in the womb when the cleft that forms to help the nourishment of the developing eye does not close properly. Coloboma commonly affects the iris when it makes the pupil look like a keyhole. One child at *Unique* has poor focus and wears a patch for one hour every day. One *Unique* baby had a cataract (clouding of the eye's lens) on one eye. One child has poor binocular vision (Biesecker 1995; Prasher 1995; Gentile 2004; Pramparo 2008; *Unique*).

## Hearing

Children usually have normal hearing although a small number have hearing loss. Two *Unique* children with a 22q12/13 duplication have a moderate hearing loss and wear a hearing aid. Two children in the medical literature (both with a 22q12 duplication) have been reported with hearing loss. Another child with a 22q13.1qter duplication has no hearing in her right ear (Barajas-barajas 2004; Boyd 2005; *Unique*).

## Feet

Although not seen in any *Unique* members, club foot (talipes) has been reported in three children with large 22q12qter duplications in the medical literature. Treatment is individually tailored and aims to straighten the foot so that it can grow and develop normally. First-line treatment is non-surgical and may include manipulation, casting, taping, physiotherapy and splinting, followed by bracing to prevent relapse. Surgery and sometimes splinting are considered if non-surgical treatments are not completely successful. The foot position may relapse as the child grows and develops, making further surgery necessary. Another child is described as having short feet and toes. One child has syndactyly (where two or more of the toes are fused together) (Jensen 1984; Rivera 1988; Prasher 1995; Pramparo 2008; *Unique*).

## Hands

Many children have hands that are unusual in some way. Unusual features vary quite a lot and are often just cosmetic – a single crease across the palm, an incurving fifth finger (clinodactyly) or fingers that are unusually short or very slender (Fryns 1980; Cantu 1981; Rivera 1988; Prasher 1995; Barajas-barajas 2004).

## Seizures

Seizures have been reported in three children, one with a 22q13.2 duplication; one with a 22q13.3 duplication and one with an interstitial duplication of 22q13.1q13.2. Seizures have not been reported in any *Unique* members (Biesecker 1995; Feenstra 2006; Pramparo 2008).

## Teeth

Generally speaking, children with chromosome disorders have a somewhat higher rate of dental problems than other children. At the same time, some children can be quite resistant to having their teeth cleaned; this can be an issue with some children who take no food orally and do not strongly associate the mouthing experience with pleasure. One child in the medical literature has malocclusion (the teeth are not aligned properly) (Gentile 2004; *Unique*).

“ She sees a dentist regularly and has nice teeth – 4 years

“ He has had to have most of his teeth out as he won't let anyone brush them – 23 years

## Behaviour

Children with a 22q12/3 duplication are typically happy, sociable, loving and affectionate. However, some children – although not all – have some behavioural issues. Hyperactivity has been described in three children described in the medical literature and one at *Unique* (all with a 22q13 duplication). One of these, a 10-year-old boy with a 22q13.1q13.2 duplication, has been diagnosed with attention deficit hyperactivity disorder (ADHD) which is characterised by restlessness and a short attention span, as well as a sleep disorder. Bipolar disorder which is characterized by mood swings and periods of aggressiveness alternating with periods of reduced initiative has been observed in some people. Other issues seen in only one child include oppositional behaviour, inappropriate friendliness to strangers and self-injurious behaviour (Prasher 1994; Gentile 2004; Boyd 2005; Feenstra 2006; Okamoto 2007; Pramparo 2008; *Unique*).

Sensory issues affect some children. One child does not like to eat certain textures and will gag when she eats them (*Unique*).

Behaviour within the autistic spectrum has been reported in one *Unique* child. 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 (*Unique*).

“ She loves little dolls and toys that she can carry around, playing with her sisters, dancing and singing. She is generally very happy and placid and a joy to be with. However, if she gets upset or frustrated she will bang her head hard on things and hit and bite herself – 2½ years

“ She is a very obedient, happy child who laughs a lot – 4 years

“ He was very aggressive to his brother when younger but now they get along very well. He loves TV, going out walking and swimming – 23 years

## Adults with a 22q12 or 22q13 duplication

To date, there are very few adults known to have a 22q12 or 22q13 duplication. *Unique* has one adult member, a man of 23 years who has a severe learning difficulty and no speech or signing. Three adults have been described in the medical literature.

A 19-year-old man with an interstitial duplication of 22q12.1q13.1 has mild learning difficulties and good speech. He is clumsy with poor fine motor skills. A 27-year-old man with an interstitial duplication of 22q11.2q13.1 has a moderate learning disability

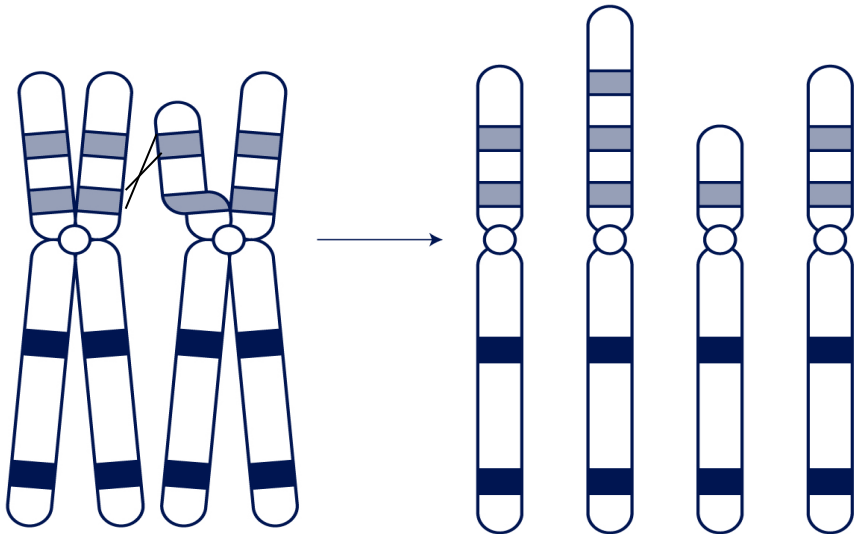
and needs help with daily living. He has lived in a long-stay centre for those with learning disabilities since he was 11 years old. A 40-year-old man with a 22q13.3qter duplication only discovered the duplication when he passed it on to his son. He has mild learning difficulties, no behavioural issues and works in a sheltered environment (Prasher 1995; Gentile 2004; Feenstra 2006; *Unique*).

## Fertility

As far as we are aware, only one person has been known to pass a duplication on to their child. A 40-year-old man (described above) passed a 22q13.3qter duplication on to his son. Neither has a speech impairment. The father has mild learning difficulties but his 4-year-old son has a moderate learning disability together with hyperactivity (Feenstra 2006).

## Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 22q12/13 duplication occurred in your child. In many of cases the 22q12/13 duplication occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 22q12/13 duplications are thought to be caused by a change that occurred when the parents' sperm or egg cells formed or possibly during copying of the early cells after the egg and sperm joined.



One way that a deletion and a duplication could theoretically arise during the formation of egg or sperm cells. On the left are two matching chromosomes, each split to the centromere and ready to pair and exchange segments. The shaded bars show similar sequences of DNA in the chromosome that enable correct pairing. But just above the centromere mispairing has occurred. When the chromosomes separate (right), the mispairing has given rise to two normal and two abnormal chromosomes, one with a deletion and one with a duplication.

Some 22q12/13 duplications are inherited from one of the parent who has an inversion on chromosome 22 (see page 4 for more information). Some 22q12/3 duplications are accompanied by a gain of material from another chromosome. This can be a *de novo* change or it can be a result of a rearrangement in one parent's chromosomes. This is usually a rearrangement known as a balanced translocation in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. Balanced translocations involving one or more chromosomes are not rare: one person in 560 has one, making a total world population of over 12 million balanced translocation carriers.

Whether the duplication is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 22q12/13 duplication and nothing you could have done would have prevented it from occurring in your baby. No dietary, workplace or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault and there is no reason for anyone to feel guilty.

### Can it happen again?

The possibility of having another pregnancy with a 22q12/13 duplication depends on the parents' chromosomes. If both parents have normal chromosomes when their blood cells are tested, the duplication is unlikely to happen again. However, if either parent has a chromosome inversion on one of their copies of chromosome 22 or carries a balanced translocation involving chromosome 22, the possibility is greatly increased of having other affected pregnancies.

Parents should have the opportunity to meet a genetic counsellor to discuss their specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all of these tests are available in all parts of the world.



*2 years 8 months*

# Inform Network Support



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Please help us to help you!

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 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 Ilse Feenstra, Department of Human Genetics, Radboud University Nijmegen Medical Centre, The Netherlands, Dr Renzo Guerrini, Children's Hospital A. Meyer and University of Florence, Florence, Italy and by Professor Maj Hultén BSc, PhD, MD, FRCPath, Professor of Reproductive Genetics, University of Warwick, UK. 2010 [SW]

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