Understanding Chromosome & Gene Disorders

22q11.2 deletion syndrome (Velo-Cardio-Facial Syndrome)

rarechromo.org

Sources

The information in this leaflet 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 2010, referenced *Unique*. When this leaflet was written *Unique* had 65 members with a pure 22q11.2 deletion without loss or gain of material from any other chromosome. These members range in age from a baby to an adult aged 55 years.

A few people, described in the medical literature and seven members of *Unique*, have a loss or gain of material from another chromosome arm as well as a 22q11.2 deletion, usually as a result of a chromosome change known as a translocation. As these people do not show the effects of a 'pure' deletion, they are not considered in this leaflet. *Unique* holds a list of these cases in the medical literature and the karyotypes of those in *Unique*; this is available on request.

Velo-cardio-facial syndrome

Velo-cardio-facial syndrome, also called 22q11.2 deletion syndrome, is caused by a small missing piece of genetic material from one copy of chromosome 22. For normal development and function, chromosomes should contain the right amount of genetic material (DNA) – not too much and not too little.

Like most other chromosome disorders, having even a small part of chromosome 22 missing may increase the risk of congenital anomalies, developmental delay and learning difficulties. However, the problems vary from person to person.

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.

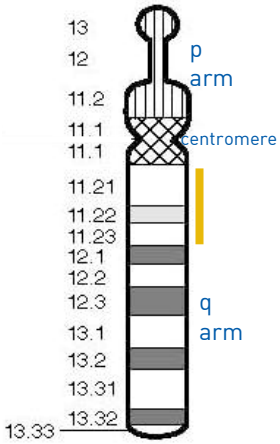
Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest in size. Each chromosome 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 Deletions

A sperm cell from the father and an egg cell from the mother each carry just one copy of each chromosome. When they join together they form a single cell that now carries two copies of each chromosome. Sometimes during the formation of the egg or sperms cells parts of the chromosomes can break off or become arranged differently from usual. People with a 22q11.2 deletion have one intact chromosome 22, but a piece from the long arm of the other copy is missing or deleted. For most people with VCFS, approximately 40 genes are missing that can affect a person's learning and physical development. 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 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 all help to determine future development, needs and achievements.

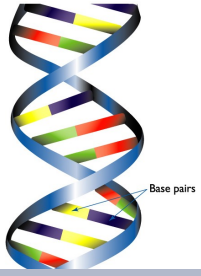
Looking at 22q11.2



Chromosomes can't be seen with the naked eye but if they are stained and magnified under a light microscope it is possible to see that each one has a distinctive pattern of light and dark bands that look like horizontal stripes. By looking at your child's chromosomes in this way, it is possible (if the missing piece is large enough) to see the points where the chromosome has broken and to see what material is missing. However, because the amount of material missing is often quite small, in this type of routine analysis your child's chromosomes may have looked normal. Consequently, there are certainly people with a 22q11.2 deletion who have not yet been diagnosed. Only molecular DNA technology can identify it. In some cases, a test known as FISH (Fluorescence *In Situ* Hybridization), specific to identifying VCFS, is used.

The most recent technique is known as microarrays (array-CGH). This shows losses (and gains) of tiny amounts of DNA throughout the chromosomes. Microarrays can show whether particular genes or bits of genes are present once, twice or three times or not at all. These very small deletions that can't be seen even under a high-powered light microscope are called microdeletions.

In the diagram of chromosome 22 above the bands are numbered outwards starting from where the short and long arms meet (the centromere). People with a 22q11.2 deletion have all, or part of the band q11.2 missing. These deletions are known as interstitial deletions, because a piece of the long arm of chromosome 22 (band q11.2) is missing but the rest of the long arm of chromosome 22 (bands q12 and q13) is still present. Band 22q11.2 contains around 3 million base pairs. This sounds like a lot but it is actually quite small and is six per cent of the DNA on chromosome 22 (one of the smallest chromosomes). Chromosome 22 has around 49 million base pairs and is about 1.5-2 per cent of the total DNA in our cells. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure.



bp = base pair
Kb = kilobase pair or 1000 base pairs
Mb = megabase pair or 1 million base pairs

VCFS or Shprintzen syndrome (Shprintzen 1978, Meinecke 1981) derives from the observations made by Dr Robert Shprintzen who noted the characteristic facial features together with heart and palate problems. It is also often called DiGeorge syndrome (Sedlacková 1955; Strong 1968; Kretschmer et al, 1968) after Dr Angelo DiGeorge who described the syndrome in the 1960s. In 1992, it was discovered that the condition referred to as velo-cardio-facial syndrome and the condition many called DiGeorge syndrome both were caused by deletions of 22q11.2 (Scambler 1992), leading to the term 22q11.2 deletion syndrome (22q11.2DS).

Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point where the chromosome has broken in your child. You will almost certainly be given a karyotype which is shorthand notation for their chromosome make-up. With VCFS, the results are likely to read something like the following example:

46, XX, del(22)(q11.2q11.2)dn

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material is missing
(22)	The deletion is from chromosome 22
(q11.2q11.2)	The chromosome has two breakpoints, both in band 22q11.2, and material between these breakpoints is missing
dn	The deletion occurred *de novo* (or as a "new event"). The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 22q11.2. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

In addition to, or instead of a karyotype you may be given the results of molecular analysis such as FISH or array-CGH for your child. In this case the results are likely to read something like one of the following examples:

46,XX.ish del (22)(q11.2q11.2)(D22S134-)

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
ish	The analysis was by fluorescent in situ hybridisation (FISH)
del	A deletion, or material is missing
(22)	The deletion is from chromosome 22
(q11.2q11.2)	The chromosome has two breakpoints, both in band 22q11.2 and material between these two breakpoints is missing
(D22S134-)	One copy of the DNA segment (marker) called D22S134 is missing

arr[hg19] 22q11.21(18894865-21808980)x1

arr	The analysis was by array-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
22q11.21	There are two breakpoints on chromosome 22, both in q11.21 and this is the region that is deleted
18894865-21808980	The base pairs between 18894865 and 21808980 have been shown to be deleted. Take the first long number from the second and you get 2,914,115 (2.91Mb). 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 22 – as you would normally expect.

Most common features

Every person with VCFS is unique and so each person will have different medical and developmental concerns. There is an enormous variability in the effects of a 22q11.2 deletion, even within the same family and between identical twins (Goodship 1995; Yamagishi 1998). Additionally, no one person will have all of the features listed in this guide. However, a number of common features have emerged:

- Heart conditions (approximately 70 per cent)
- An abnormality of the palate resulting in nasal speech (approximately 70 per cent)
- Characteristic facial features
- Low levels of calcium in the blood, called hypocalcaemia (which can result in seizures)
- Feeding difficulties
- Kidney problems
- Development and speech delay
- Variable difficulties in learning and cognition, ranging from mild (most cases) to more severe. Children will often need support with learning, although the amount of support needed by each child will vary
- Immune system difficulties
- Growth may be at a different speed from the general population, but adult height is almost always normal
- Behavioural, emotional and psychiatric disorders including attention deficit hyperactivity disorder, generalized anxiety and in the most severe cases, psychosis

How common is 22q11.2 deletion syndrome?

It is the most commonly occurring chromosome deletion syndrome and the second most common genetic cause of congenital heart defects. Congenital means a condition which a child is born with. It is reported to affect 1 in 2000 people and there have been more than 1500 cases reported in the medical literature worldwide. The deletion occurs with equal frequency in males and females. Despite the prevalence VCFS is often underdiagnosed because the features can be mild and/or highly variable. The condition may actually be more common than this estimate, however, because some people with a 22q11.2 deletion are not diagnosed with the disorder (Shprintzen 2008; Green 2009).

Are there people with 22q11.2 deletions who are healthy, have no major medical problems or birth defects and have developed within the normal range?

Yes, there are. Some people with a 22q11.2 deletion are affected very mildly. Some parents of children with 22q11.2DS have the same deletion but do not have any obvious unusual features or delayed development. The signs in other parents with the deletion are so subtle that they have not been diagnosed until later life following the birth of a child with more obvious features. Some children with 22q11.2DS may also be mildly affected.

What is the outlook?

There are some reports in the literature of neonatal death, most commonly due to severe cardiac problems. Progress in the management of cardiac disease has improved the prognosis of babies with cardiac anomalies, and the vast majority of babies with VCFS have successful corrections of their heart problems (either with time or surgery). Immune problems generally subside with time and speech problems respond well to speech therapy and if necessary surgery. For children with no serious heart or other organ problems, lifespan should not be significantly affected and there are many adults reported in the medical literature (see Adults with VCFS page 18).

" Her general health is very good. She is happy and healthy **"** – *8 years*

Pregnancy and birth

Most mothers carrying babies with VCFS experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, as cardiac defects and/or a cleft palate are common in 22q11.2DS, babies who have these anomalies detected on a prenatal ultrasound sound scan in the second trimester may have their chromosomes tested (either by amniocentesis or chorionic villus sampling (CVS)). The published medical literature contains many examples of prenatal diagnoses of VCFS (Goktolga 2008; *Unique*).

Three *Unique* mothers reported polyhydramnios (an unusually high volume of amniotic fluid) during pregnancy. Polyhydramnios can result in a premature delivery due to overdistension of the uterus. Polyhydramnios has also been reported in the medical literature (Vantrappen 1999; *Unique*).

Growth and feeding

4 years

Babies are not typically small and underweight at birth and birth weights recorded at *Unique* show a considerable variation with an average of 2.92 kilos (6lb 7oz). Around a quarter of the *Unique* babies had a low birth weight (below 2.6 kilos or 5 lb 12oz) at term (*Unique*).

Range of birthweights at *Unique* (at or near term):
1.871 kilos (4lbs 2oz) to 3.997 kilos (8lb 13oz)

Although children are often short, many of them catch up after puberty and attain a normal adult height. However, in a study of 95 children between the ages of one and 15 years, almost half were small in comparison to their peers with around four per cent being very small. Many *Unique* children have had slow weight gain and are small and of slim build (Weinzimer 1998; *Unique*). However, their growth proceeds more normally in adolescence and nearly all people with VCFS reach adult height in the normal range. One issue that may affect growth more severely is the presence of severe pulmonary valve or artery anomalies. Very few cases are treated with growth hormone.

Feeding difficulties, especially in the new-born period, are a major area of concern for families, affecting around 30 per cent of those with VCFS.

Many families have found that a feeding specialist is often helpful. Feeding problems include food coming through the nose (nasal regurgitation) because of the palatal weakness and gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). In the *Unique* survey, almost a third of babies had reflux. 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. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, a few babies may benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (McDonald-McGinn 2004; *Unique*), but this should not be necessary in most cases.

3 years

The hypotonia that is common in babies with VCFS can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft palate can also find the action of sucking and swallowing difficult. Several of the mothers surveyed by *Unique* successfully breastfed their babies. A number of *Unique* babies benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat).

As some of these babies matured enough to suck effectively, the NG-tube could be removed and breast or bottle feeding established. Several other babies who initially benefited from temporary NG-tubes later needed gastrostomy tubes (a G-tube, feeding direct into the stomach) in order to meet their nutritional needs (*Unique*).

Some older babies and toddlers have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers and the start of finger feeding may be delayed. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems. As a result of these feeding difficulties a number of families have consulted a dietician. Many families report that feeding difficulties often resolve by school age (*Unique*).

❝ He has nasal regurgitation. He has a sub-mucous cleft palate and a poor suck reflex. Whenever we went to the next stage of feeding he struggled with solids and gags on bits. He vomits a lot when introduced to something new. ❞ – *4 years*

Appearance

Children with VCFS may look similar, although the facial characteristics noted are often very subtle and are actually variants of normal. They often have a small mouth and chin, a broad bridge to the nose, and sometimes small ears with over-folded or thickened rims. Facial features change with age and the nose may become slightly more prominent in adulthood. Other features may include a slightly open mouthed expression and abundant scalp hair.

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

Some people with VCFS will have entirely normal development, but often they are a little slow to reach their developmental motor milestones with delays in learning how to crawl and walk in comparison to other children. This could be due to your child being very sick and spending time in hospital or be due to problems associated with the deletion such as poor motor skills, muscle tone (hypotonia) and lack of co-ordination. Hypotonia affects most children with VCFS and often improves as children mature; nonetheless, early physiotherapy and occupational therapy can be beneficial. Some children will only have mild delays others will have more significant problems. The *Unique* experience is that babies start to roll between 3 months and 12 months (average 8 months); sit between 6 months and 20 months (average 10 months) and crawl between 6 months and 21 months (average 13 months). Independent walking was mastered between 12 months and 2 years 10 months (average 19 months).

The average age for walking for children with VCFS in the medical literature is 12 months, although many children walk later and up to 18 months is considered normal. The majority of children go on to walk, skip, hop, climb stairs and run, although they can be unsteady with poor balance (Fine 2005; *Unique*).

❝ He is fast crawling and now starting to walk. He climbs everything! ❞ – *20 months*

❝ She is fine sitting, walking and running (sort of), can jump (just) and can walk up the stairs holding on to the rail. Outdoors she is a bit more wobbly – I think we are also more nervous of her falling down and hurting herself outside. She is confident walking and running on grass, but uneven pavements are more tricky. ❞ – *3 years*

❝ She has no mobility problems. ❞ – *8 years*

❝ Her mobility is fine although she is slow with stairs. ❞ – *25 years*

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

Hypotonia can also affect fine motor skills in children with VCFS 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*).

Toilet training may also be affected. The information at *Unique* shows that consistent toilet training was mastered between 2 years and 16 years (average 3½ years) (*Unique*).

“ She is only in nappies at night now. Her fine motor skills have been assessed as being better than her gross motor skills, but she does lack some fine control, for example manipulating puzzle pieces or pins into holes on a board. She has no trouble holding cutlery, bottle or toys and she holds a pencil perfectly already! **”** – *3 years*

“ As a young baby he needed help holding his bottle until he was 8 months. He is still in nappies day and night. **”** – *4 years*

“ She has no problems with fine motor skills, she is not in nappies, she can wash and shower alone, brush her teeth and hair. She is a normal 8-year-old. **”**

“ She had some small motor issues for example with zips and buttons but worked with an occupational therapist. She took longer than usual to potty train. **”** – *10 years*

“ He was in nappies at night until 9 years. **”**

“ She has a strange way of holding pencils and pens. **”** – *25 years*

“ She has a slight tremor and tends to be a bit clumsy. **”** – *31 years*

Speech and communication

Many children with VCFS learn to speak well. However, speech is often mildly delayed. This may be due to hypotonia, palate or ear problems. Typically, children with VCFS develop first words around the age of 18 months to two years but then do not reach the next stage of language development (short phrases and sentences) until between the ages of three and five years. Those with a cleft palate or other palate problems have specific difficulty with certain sounds. In approximately 70 per cent of those with VCFS speech is hypernasal making it harder for them to be understood. As a result of not being understood, parents and carers may not reinforce early speech attempts. The most common articulation pattern in children with VCFS is the development of glottal stop substitutions for sounds requiring oral pressure. This is a type of articulation error, often confused for an omission, where a sound is articulated in the larynx (sounding like a cough) and substituted for a sound normally articulated in the oral cavity. In VCFS, glottal stops are often substituted for all other consonants except m, n, and ng. In general, expressive speech is particularly affected in children with VCFS, while receptive language skills are stronger, although still impaired. Expressive language tends to increase after four or five years of age when both speech therapy and palate surgery have taken place.

However, articulation problems may persist if not correctly treated (Fine 2005; Baylis 2008; Shprintzen 2008; *Unique*).

“ He uses gestures, vocal noises, pointing and signing. He is just starting to talk. **”** – *20 months*

“ She uses talking to communicate and a handful of signs. She had initial speech delay and her speech is still significantly delayed especially in sound production. Her expressive language is worse than her receptive language. In fact her receptive communication skills have recently been measured as average for her age. In terms of teaching her speech, it is all about repetition. Specific speech sound work in a fun and engaging manner has worked for her. **”** – *3 years*

“ He speaks in two-word phrases and most of the time it is hard to make out what he is saying without him showing or taking a person to what he is talking about. **”** – *4 years*

“ She started speaking at 7 years. She uses signs, gestures and some speech. She can speak in full sentences but most of it is not understandable. **”** – *8 years*

“ She was delayed in communicating feelings and emotions. She needed lots of therapy to use words versus aggression or rages. **”** – *10 years*

“ He mostly uses full sentences but sometimes uses the wrong tense. His speech is slightly nasal. **”** – *11 years*

“ He has no speech problems, although uses short sentences and tends to answer questions rather than begin a conversation. **”**– *18 years*

“ She speaks in complex sentences. She sometimes has trouble with words but usually finds a suitable one. Her speech is nasal and people used to find it hard to understand her. **”** – *20 years*

“ She speaks fine! Initially her speech was very nasal. **”** – *25 years*

Learning

The average IQ in children with VCFS has been reported to be in the mid-70s in many recent studies. This average score compares to the average score of 100 in the general population. IQ scores of 80 – 120 are considered to be the normal range. This means that slightly more than half of children with VCFS have lower than normal IQs although almost half have an IQ in the normal range. However, nearly all people with VCFS have specific learning disabilities, primarily in the areas of problem solving, reading comprehension and mathematics. These specific learning differences result in many children requiring special help in school. Most children will attend mainstream school (almost three quarters of *Unique* children) but may need some classroom assistance or special needs lessons. The other 20 – 30 per cent of children benefit from a special education school. Two independent studies have suggested girls with VCFS are less likely to have difficulties than boys. This is an area that needs further research (Antshel 2005; Fine 2005; Okarsdottir 2005; Roizen 2007; *Unique*).

As a result of these specific learning differences, most children have relative strengths in reading, spelling and rote memorisation but more difficulty with complex maths, abstract reasoning and problem solving. A study of 50 children with 22q11.2DS and another of 90 adolescents with VCFS both reported that reading and

spelling were in the low-average range (Woodin 2001; Antshel 2005). Although children with VCFS have relative strengths in reading decoding, they may struggle with comprehension and therefore may find it hard to read to learn.

They often have difficulty with time concepts, shape, colour and size. They can also have disorganised thinking and become obsessed with one topic or idea. Abstract reasoning may be problematic as children tend to think literally. The evidence suggests that children with VCFS have stronger verbal than visual memory skills and stronger reading than maths skills and are often described as having a non-verbal learning disorder. They are visual learners who prefer to watch and copy, rather than problem solve. Specific teaching methods utilising these skills can be implemented in order to maximise learning. Small group or individual instruction is beneficial. Instructions should be clear and specific, using short sentences and repeating key words. Children benefit from a lot of repetition and routine and computer-aided learning may help. They also do well with music and learning using musical templates can be an important tool (Shprintzen 2000; *Unique*).

4 years 3 months

A recent study of 172 people with 22q11.2DS aged from 5 to 54 years suggests that there is a decline in IQ as children and adolescents enter adulthood (Golding-Kushner 1985; Green 2009). This is an area that needs further research.

❝ He loves the computer and learns computer games all by himself. Anything that is electronic he can figure out quickly. ❞ – *4 years*

❝ She struggles with maths but she is strong in reading, PE and music. ❞– *8 years*

❝ She has support in school to help her academically and with her behaviour. She needs routine and structure and clear expectations to be successful. Her maths skills took off when she learned to ice skate through Special Olympics! Her art skills are fabulous. She is now a very hard worker which helps her become more successful. ❞ – *10 years*

❝ He is in a special educational needs unit attached to a mainstream school. He struggles with technical subjects such as maths and science, but is better at English, art etc. He reads books for younger children and can draw and write (not very tidily but OK). ❞ – *11 years*

❝ He is now 18 with a spelling age of 12. He finds numeracy very difficult but managed a few GCSEs. He is now at agricultural college. ❞ – *18 years*

❝ Her strengths are music, art and textiles, social awareness and drama. She has 3 A levels and is at university. She reads anything from text books to novels. ❞ – *20 years*

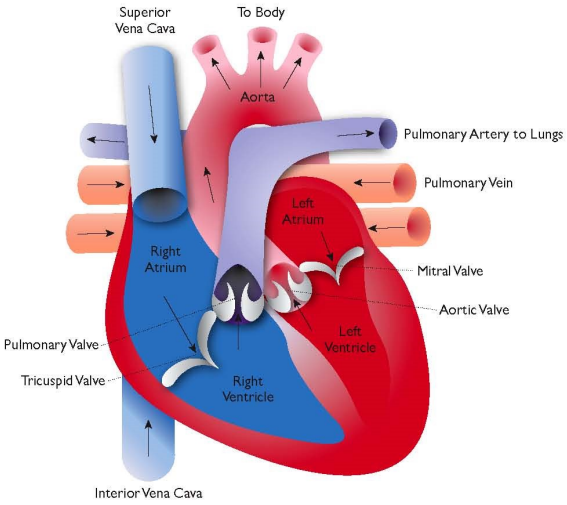
❝ She was in mainstream school throughout and obtained a C in GCSE art. She is hopeless at maths, but good at English. ❞ – *25 years*

❝ She is good at art and enjoys reading soap-style magazines. ❞ – *31 years*

Most likely features

Heart problems

VCFS is the second most commonly seen chromosome disorder in congenital heart disease after Down's syndrome. Heart problems are reported in around 70 per cent of those with VCFS and these heart conditions have often been the trigger for the genetic testing which resulted in the diagnosis of VCFS (McDonald-McGinn 1999; Repetto 2009; *Unique*).



A normal heart

Due to the prevalence of heart conditions in VCFS babies and children should have their hearts checked. The investigations usually take the form of an echocardiogram, (which is a detailed ultra sound scan of the heart using a machine very similar to those used during pregnancy), or an electrocardiogram (which monitors the heart beat).

These are not invasive procedures and are completely harmless and painless. If a heart defect is discovered some babies and children will require surgery to correct the problem, often in the new-born period. If your child has not been diagnosed with a heart defect as a baby, minor changes may be found in later life, so follow-up cardiac assessment even in children who are not known to have heart problems is recommended. Most of these later changes are minor.

The most common cardiac defects in VCFS are septal defects, but the most obvious and easiest to detect anomalies in VCFS affect the main outflows of the heart such as the aorta and the pulmonary arteries, with tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch being the most common. The heart problems diagnosed in individual children may be single or multiple (McDonald-McGinn 1999, Carotti 2008; *Unique*). They include:

Tetralogy of Fallot (reported in 22 per cent of those with VCFS, and about 15 to 25 per cent of all TOFs are cases with VCFS). A complex heart condition involving both a VSD (see page 13) and an obstruction just below the valve in the artery that leads to the lungs. Blue (deoxygenated) blood cannot easily get to the lungs to pick up oxygen and some of it flows through the hole into the other pumping chamber from where it is pumped around the body. If there are no other risk factors, more than 95 per cent of babies with tetralogy of Fallot successfully undergo surgery in the first year of life.

Interrupted aortic arch (reported in 15 per cent of those with VCFS). The aorta is the main blood vessel that carries oxygen-rich blood away from the heart to the organs

of the body. After it leaves the heart, it first ascends in the chest to give off blood vessels to the arms and head. Then, it turns downward, forming a semicircular arch, and heads toward the lower half of the body. An interrupted aortic arch is the absence or discontinuation of a portion of the aortic arch.

Ventricular septal defects (VSDs) Holes in the wall between the two pumping chambers 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.

Truncus arteriosus (reported in seven per cent of those with VCFS) Instead of having separate blood vessels leading out of each side of the heart, a baby with a truncus arteriosus has a single blood vessel leaving the heart that then branches into vessels that go to the lungs and the body. This great vessel usually sits over both the ventricles and the upper part of the wall between the two chambers is missing, resulting in a VSD. Early surgical repair is usually needed.

Vascular ring (reported in five per cent of those with VCFS) Abnormal formation of the aorta (see diagram on page 12) and/or its surrounding blood vessels.

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.

Aortic arch anomaly. These anomalies arise from unusual patterns of development of the aortic arch arteries, such as persistence of prenatal vessels that normally regress, and degeneration of vessels that normally continue to develop.

Others include pulmonary stenosis (the entrance to the artery that takes blood to the lungs is unusually narrow. The narrowing usually affects the pulmonary valve and the pulmonary artery itself); hypoplastic left heart syndrome (the left side of the heart has not developed properly and is very small); bicuspid aortic valve (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).

Palate

This is one of the most common areas affected in VCFS with around seventy per cent of children having some kind of palate (roof of the mouth) anomaly. The types of problems are very variable and can often be a combination of anomalies. The most common problem is velopharyngeal insufficiency (VPI) affecting about 70 per cent of people with VCFS. The velopharyngeal mechanism is responsible for directing the transmission of sound energy and air pressure in both the oral cavity and the nasal cavity. When this mechanism is impaired in some way, the valve does not fully close, and VPI can develop. VPI may be a structural problem (short palate), a functional

problem (hypotonia of the velopharyngeal muscles), or a combination of the two. Sometimes the palate does not form correctly during development. This results in an opening in the roof of the mouth. Cleft lip occurs when the tissue that forms the upper lip does not fuse during prenatal development and is found only occasionally in VCFS.

A cleft palate can contribute to the early feeding difficulties seen in children. At least 25 per cent of people with VCFS have a bifid uvula (the uvula, the little V-shaped fleshy mass hanging from the back of the soft palate, is split).

Babies with palate anomalies often have vomiting through the nose and later have hypernasal speech which makes it difficult for the child to be understood (see Speech page 9).

Immunity

Many babies and children with VCFS often experience recurrent infections caused by problems with their immune system. In babies and young children, the immune system is controlled by the thymus gland in the chest and sometimes this can be partially or completely absent or just not work well. Again the symptoms can be mild or severe. Often children are just more susceptible to colds and viral infections and fungal infections. Children who are frequently ill should have their immune system checked and those with a problem should be referred to an immunologist. Care should be taken with immunisations and live vaccines should be avoided in children with severe immune system problems. Most children improve with age, but some continue to be affected into later childhood and adulthood. Some children develop autoimmune diseases related to their immune deficiency, such as juvenile rheumatoid arthritis (which affects five *Unique* members), idiopathic thrombocytopenia (low platelet count), vitiligo (depigmentation of patches of skin) and Graves disease (an overactive thyroid) (Smith 1998; Sullivan 1999; Davies 2001; Sullivan 2004; *Unique*).

Hypocalcaemia (calcium deficiency)

Calcium is important to the body in the firing nerve endings and muscles. More than half of all children with VCFS have calcium levels within the normal range, however less than half of all children with VCFS are hypocalcaemic (low calcium levels). This may cause jitteriness or in severe cases seizures in young children, or muscle cramps or tingling of the mouth and fingers. As a result, it is likely your baby's calcium levels will be monitored. This problem is caused by anomalies of the parathyroid gland which produces a hormone called parathyroid hormone (PTH). The low calcium levels usually resolve in infancy with most children outgrowing this problem by their first birthday, however, some children require calcium supplements for a longer period of time. Milder symptoms can be treated by a milky drink at bedtime. Recurrence of hypocalcaemia in later childhood has been reported during illness and/or puberty when medication may again be needed. It is unlikely that your child will develop hypocalcaemia in later childhood if they do not suffer from it as a small baby (Van den Bosch 2002; Repetto 2009; *Unique*).

Kidney and urinary tract

Around a third of children with VCFS have differences in the way their kidneys are

formed or how they work, such as a single or malformed kidney or kidney (vesico-ureteral) reflux (where the urine flows upwards from the bladder back up to the kidney, potentially damaging the kidneys). In addition, some children have urinary tract infections or bedwetting (Wu 2002; *Unique*).

Seizures

Seizures are seen in both children and adults with VCFS. Seizures may have a number of possible causes including hypocalcemia, but in most cases, seizures in VCFS are neurologically based and may be accompanied by abnormal EEG recordings. Seizures can start at any time in life and vary from mild periods of "blanking out" to severe grand mal events. For the majority of children, seizures are well-controlled with medication.

Vision

Eye findings in VCFS are common and include tortuous retinal vessels, small optic discs, small eyes, clefts in the iris (colobomas), and strabismus where one or both eyes can turn inwards, outwards or upwards.

Hearing

Some children with VCFS have a hearing impairment. The most common is a conductive hearing loss caused by fluid in the middle ear (glue ear or serous otitis media). Glue ear usually resolves as children get older secondary to growth and an improving immune system. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, if glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum. Sensori-neural hearing loss has also been reported in one child at *Unique* and in the published medical literature (*Unique*).

Bones and skeleton

Abnormalities of the vertebrae of the spine are common in VCFS and may require surgery. The most common problem is one of curvature of the spine (scoliosis), but abnormalities of the individual vertebrae also are found. Extra ribs, extra fingers and toes; differences in wing bones (scapula); and occasionally premature fusion of the bones of the skull (craniosynostosis) occur infrequently and can be addressed surgically if needed. Some children have tapering fingers. Many children suffer leg pains and cramps during the night or on resting from exercise. This can be due to tight ligaments in the legs or abnormalities of the foot or ankle joints but in most cases the cause is unknown. This can often be treated by muscle stretching exercises and/or orthotic insoles in their shoes. Several *Unique* children have second toes that either stick upwards or overlap their third toes (Ryan 1997; *Unique*).

Digestion

One problem is constipation which affects three quarters of *Unique* children with VCFS and has also been reported in the medical literature. Dietary changes and/or medication can help to manage the problem (Ryan 1997; *Unique*).

Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers. Dental problems seen at both *Unique* and in the medical literature include poor tooth enamel, excess dental cavities and crooked teeth. Regular and high quality dental care is recommended (Ryan 1997; *Unique*).

Genital anomalies

Minor anomalies of the genitals are common in babies with VCFS, most often affecting boys. The most common problem is cryptorchidism (undescended testes). The testicles can be brought down by a straightforward surgical operation if they do not descend of their own accord in time. Hypospadias (where the opening of the penis is not at the tip) is also common (Ryan 1997; *Unique*).

Much less commonly an absent uterus in girls has been reported (Unique).

Behaviour

Social skills are often underdeveloped making it more difficult for children with VCFS to make friends. Their small size and unclear speech may contribute to these problems. Children are generally more at ease in familiar situations and with people they know well. Children with VCFS are often shy, immature, impulsive, overly gullible and suffer from mood swings. They can also be particularly 'clingy' children showing a particular attachment to their mother or other care-givers (Vogels 2002; *Unique*).

Additionally, affected children are more likely than children without VCFS to have attention deficit hyperactivity disorder (ADHD) which is characterised by restlessness and a short attention span. Around a third to half of children with 22q11.2DS are reported to have ADHD. Autistic spectrum disorders have also been reported in 14-45 per cent of children and adolescents with VCFS and a full-blown autistic disorder was found in five to 11 per cent (Fine 2005; Antshel 2007; Jolin 2009; *Unique*). 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. Although the majority of children with VCFS do not require medication to treat behavioural disorders, some reports suggest that ADHD can be treated successfully with medication (Gothelf 2003).

Later in life during adolescence and adult years, people with 22q11.2DS are at an increased risk of developing mental health problems such as depression, anxiety, obsessive compulsive disorder, schizophrenia and bipolar disorder (Yamagishi and Srivastava 2003; Prasad 2008). VCFS is the single most significant genetic risk factor yet identified for the development of psychosis.

Anxiety and depression have been found in adolescents with VCFS suggesting that the combination of puberty and increased social pressure puts people with VCFS at an increased risk of developing anxiety and depressive disorders (Swillen 1999).

Obsessive compulsive disorder (OCD) is an anxiety disorder characterized by intrusive thoughts that produce anxiety, by repetitive behaviours aimed at reducing anxiety, or by a combination of such thoughts (obsessions) and behaviours (compulsions). One study of 43 people suggested that around a third had OCD (Gothelf 2004).

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 (Bassett 2008).

Bipolar disorder (BPD), previously known as manic-depressive illness, is estimated to occur in around one per cent of the general population. It is classically defined by cyclic periods of high and low energy where the person's mood may become excited, elated or irritable. These mood states which can last hours to weeks are usually accompanied by an alteration in the sleep-wake cycle, excessive talkativeness, impulsive and compulsive behaviours, changes in appetite, and distractibility in thinking. The high states (hypomania or mania) are usually followed by periods of depression, marked by a sad or irritable mood, low energy, loss of interest in things that ordinarily give pleasure, insomnia or sleeping too much, and appetite loss or cravings for sweets and carbohydrates. BPD can be treated using a combination of medication and learning to recognise what triggers an episode or learning to recognise the signs of an approaching episode (Jolin 2009).

Although the majority of people with VCFS do not develop schizophrenia or BPD, the risk for psychiatric illness is 25 times higher for people with VCFS than the general population. Therefore, it is recommended that all those with VCFS should be screened for predictive symptoms of psychiatric illness to enable early diagnosis and treatment (Shprintzen 2008). Treatment of psychosis in VCFS using common psychiatric medications often fails, and the use of medications that reduce levels of dopamine in the brain has been suggested (Graf 2001; O'Hanlon 2003).

❝ He is very happy, loving and sociable. ❞ – *20 months*

❝ She has a really charming personality. Initially she can be shy but if she takes a shine to someone then she really takes a shine and can be really engaging. She is (most of the time) a smiley, happy and delightful little girl. ❞ – *3 years*

❝ He can be very loving. He is shy and hyperactive and can be very obsessive. He has certain phobias, for example he is scared of huge areas and crowds and loud voices or noises. ❞ – *4 years*

❝ She used to be an angry, rageful, aggressive kid but now is very loving and snugly – medication, therapies and growth have helped! She has come a long way! She still has some anxiety issues. ❞ – *10 years*

❝ She has no behavioural problems. ❞ – *8 years*

❝ He can be very loving and caring at times and is usually polite. Getting him to go to bed can sometimes be difficult. ❞ – *11 years*

3 years

❝ He generally has no behavioural problems although can be depressed – gets up, bangs doors, thumps desk, refuses to get dressed – but can also be lovely. ❞
– *18 years*

❝ Her behaviour is good but she gets stressed in towns and supermarkets. ❞
– *20 years*

❝ She has a kind nature and a good sense of humour. She has had mental health problems including psychotic depression in her twenties and has ongoing support from the mental health team. She has recently had a breakdown and is now responding well to specialised treatment in a psychiatric unit. ❞ – *31 years*

Sleep

Sleep problems affect many children with VCFS and there are multiple contributing factors including anxiety, leg pains, obstructive breathing problems, and a variety of psychiatric disturbances. Some children find it hard to settle at bedtime and consequently fall asleep late; others continue to have night-wakings throughout childhood.

Puberty

The evidence in the published medical literature and at *Unique* suggests that puberty generally proceeds as normal at the usual age.

Adults with VCFS

There are many adults with VCFS, a number of whom are mildly affected and only discovered they had VCFS when their child was diagnosed. However, as in children with VCFS there is a wide variation in how adults with VCFS are affected. One clinic in the USA has a number of adults in their 70s and at least one in their 80s (Shprintzen 2008).

Unique has 19 adult members with 22q11.2DS. An 18-year-old young man obtained a number of GCSEs and now attends agricultural college. He has no behavioural problems although he can get depressed and has low self-esteem. Another 19-year-old young man is active and impulsive and sometimes suffers bouts of depression. A 20-year-old girl has 3 A Levels and is currently in her second year at university and is an exchange student spending a year in the USA. Her speech was initially delayed but is fine now. Her strengths are music, art and textiles and drama. She has a very strong sense of justice and loves books, music and theatre. She has a best friend and is also very close to her sister. A 21-year-old has grown into a lovely young woman with a very full and interesting life. She is at college studying a childcare course and wants to be a special needs classroom assistant. A 25-year-old woman obtained a GCSE in art. She is good at art, music and English and has a good memory but finds maths difficult – she struggles with money and anything to do with numbers. She loves to read magazines and novels. She has attended a life-skills course and is now a volunteer at a playgroup and lives at home. She goes to an art group once a week and belongs to a Ranger Guide unit. She suffers from anxiety, depression and panic attacks. A 31-year-old woman has completed a computer course at college and is good at pottery and art and enjoys reading magazines. In her late teens, she became depressed and suffered mental health problems and low self

-esteem. She has a good spirit and wants to have a social life. She loves watching TV (especially soap operas) and has a kind nature and a good sense of humour. She has psychotic depression and takes anti-psychotic medication (*Unique*).

One study of 78 adults with VCFS found that eight per cent had normal intelligence; around 50 per cent had borderline normal intelligence; around a third had mild learning difficulties and just fewer than eight per cent had moderate learning difficulties (Bassett 2005). Another study involving19 adults with 22q11.2DS showed that they performed less well than their peers on tasks social comprehension and planning, but there were no differences on tests of attention, verbal fluency or learning/memory (Henry 2002). Another study focussed on those adults who were diagnosed with VCFS after their child's diagnosis. Of the 19 adults (aged 20-52 years) in this study, two thirds graduated high school, almost all the mothers were homemakers, and fathers' occupations included a maintenance worker, security guard and a milkman (McDonald-McGinn 2001).

One of the main areas of study of adults with VCFS has been centred on schizophrenia (see Behaviour page 16) (Chow 2006).

Why are people with VCFS so different from each other?

We don't understand this properly yet but a person's genes and environment play a role.

Ongoing research involving 22q11.2

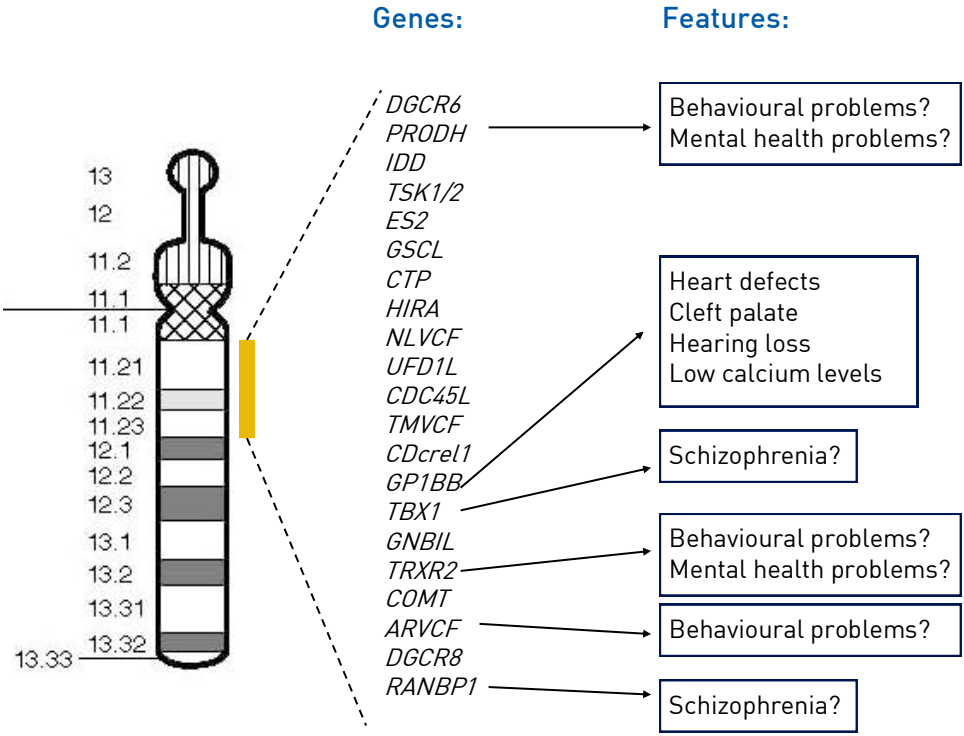
The features of VCFS are likely to be a result of the loss of a number of different genes found in this region. Most commonly (in almost 90 per cent) people with VCFS have a 3 Mb deletion in the region 22q11.2 containing around 30 to 40 genes (Lindsay 1995; Carlson 1997; Shaikh 2000). This is often referred to as the typically deleted region (TDR). However, a small number of people have a smaller deletion of 1.5 Mb or other atypical deletions including around 24 genes (Fernandez 2009). There have been attempts to try to correlate the size and region of the 22q11.2 deletion with the features of VCFS, but no strong correlation has been found. However, there is a wide variation of features, even within families where the same deletion is shared.

Researchers are taking a multi-faceted approach in order to further understand VCFS which includes studies of people with 22q11.2, studies of the potential genes involved and studies using mice. Not all of the 30 to 40 genes in the region have been well characterised. However, researchers have determined that the loss of a particular gene on chromosome 22, *TBX1*, is probably responsible for many of the syndrome's characteristic signs (such as heart defects, a cleft palate, distinctive facial features, hearing loss, and low calcium levels). The *TBX1* gene provides instructions for making a protein called T-box 1. Genes in the T-box family play important roles in the formation of tissues and organs during embryonic development. The T-box 1 protein appears to be necessary for the normal development of muscles and bones of the face and neck, large arteries that carry blood, structures in the ear and glands such as the thymus and parathyroid. However, it should be noted that as many as 25-30 per cent of people with VCFS and a deletion of *TBX1* do not have cardiac problems suggesting that *TBX1* contributes but is not sufficient to the heart problems. Some studies suggest that a deletion of

this gene may contribute to behavioural problems as well (Prasad 2008; Scambler 2010).

The loss of another gene, *COMT*, in the same region of chromosome 22 may also help explain the increased risk of behavioural problems and mental health problems (Prasad 2008). The *COMT* gene provides instructions for making an enzyme called catechol-O-methyltransferase which is active in the brain and other tissues. Mice who have *COMT* deleted display impaired emotional behaviour. Variations in the *COMT* gene are among many factors under study to help explain the causes of schizophrenia and other behavioural problems seen in VCFS. A large number of genetic and lifestyle factors, most of which remain unknown are also likely determine the risk of developing these conditions. However, *COMT* is also thought to interact with sex hormones (for example oestrogen) which may contribute to the onset of psychiatric disorders in VCFS during adolescence and young adulthood (Gogos 1998; Gothelf 2005).

PRODH might also be involved in the behavioural and psychiatric problems seen in 22q11.2DS. Mice with *Prodh* missing have a problem with attention focussing (Gogos 1999).



Other potential genes involved in VCFS include *DGCR8*, *ZDHHC8* and *GNB1L*. Mice missing *Dgcr8* have behavioural deficits similar to those seen in VCFS (Stark 2008); while *ZDHHC8* and *GNB1L* have both been linked to schizophrenia in (Liu 2002; Paylor 2006). Additional genes in the deleted region likely to contribute to the varied features of VCFS.

It is important to remember that while identifying the gene(s) responsible for certain features of VCFS is interesting 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 did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 22q11.2 deletion occurred. In the vast majority of cases (more than 90 per cent) the 22q11.2 deletion occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 22q11.2 deletions are caused by a change that occurred when the parents' sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined (Bassett 2008).

In the other approximately 10 per cent of cases, one of the parents has VCFS and has passed it on to their child. Because the physical findings associated with VCFS can be subtle and vary from person to person, even within a family, often a parent does not know they have the syndrome until their child is diagnosed. A small minority of 22q11.2 deletions are accompanied by a gain of material from another chromosome and are often the 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 500 has one, making a total world population of over 13 million balanced translocation carriers.

Whether the deletion is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 22q11.2 deletion and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault.

Can it happen again?

The possibility of having another pregnancy with VCFS depends on the parents' chromosomes. If both parents have normal chromosomes when their blood cells are tested, the deletion is very unlikely to happen again. However, there is a very small possibility that the deletion occurred during the formation of the egg or sperm cells in a parent. When this occurs there is a tiny chance that parents with apparently normal chromosomes could have another affected pregnancy. However, if either parent has a chromosome rearrangement or deletion involving 22q11.2, 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. Scans of the developing baby's heart (fetal echocardiograms) may also be helpful in monitoring a pregnancy with an increased risk of VCFS.

If one person in a family with VCFS 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.

Will my child with VCFS have similarly affected children?

Your child with VCFS may well want to have children. It is thought that people with the syndrome have normal fertility. 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. Prenatal diagnosis is available to determine if a pregnancy is affected (see above). Their ability to look after a child is very likely to be closely related to their own learning ability.

A star in a Christmas nativity play

What families say.....

❝ These kids have sunny, chirpy personalities, they are charming, engaging, warm and they can laugh a lot and know how to enjoy themselves! ❞

❝ He is very happy, loving and sociable. ❞

❝ She tries everything in an attempt to prove doubters wrong. ❞

❝ She is happy and healthy. ❞

❝ She is very special. ❞

❝ He has given us a sense of what is important - we don't stress the small stuff anymore. He has taught us so much. ❞

Inform Network Support

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

Max Appeal

Supporting families affected by DiGeorge syndrome, VCFS and 22q11.2 deletion
www.maxappeal.org.uk

Support for Disorders of Chromosome 22

www.c22c.org/

In the UK, the NHS has produced a personal health record specifically for those affected by 22q11.2DS. The UK also has several specialist multidisciplinary clinics for people with 22q11.2DS . Your clinical geneticist can advise if there is a clinic in your region

Join Unique for family links, information and support.

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

Please help us to help you!

Unique lists other organisations websites to help families looking for information. This does not imply that we endorse their content or have 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. Robert J. Shprintzen, Velo-Cardio-Facial Syndrome International Center, Upstate Medical University, USA, Dr Helen V Firth, Addenbrookes Hospital, UK and by Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK 2011. (SW)

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