Support and Information

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This guide was developed by Unique with generous support from the James Tudor Foundation.

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This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Dr Melissa Carter, Clinical Geneticist specializing in developmental disabilities at The Hospital for Sick Children in Toronto, Canada , and by Professor Maj Hultén, Professor of Medical Genetics, University of Warwick, UK and Karolinska Institutet, Stockholm, Sweden.
The CAKUT (congenital anomalies of kidney and urinary tract) information in this guide was updated in 2021 by Dr. Emily Groopman, MD/PhD (Broad Institute of MIT and Harvard, Cambridge, MA, USA; Boston Children's Hospital, Boston, MA, USA)
Version 1 2011. Version 2 (PM) 2016. Version 2.1 (AP) 2021. Version 2.11 (AP) 2025.

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Understanding Chromosome & Gene Disorders

22q11.2 duplications

22q11.2 duplications at a glance

People with the typical 22q11.2 duplication have a very tiny extra bit of chromosome 22.

Any effects of having this extra bit of chromosome 22 appear to be generally mild and highly variable, even within the same family.

At the moment, it's uncertain whether the 22q11.2 duplication is a natural genetic variant - we are all different - or whether it's a real syndrome whose effects can be highly variable.

About 70 per cent of people with the extra bit of chromosome 22 have inherited it from one of their parents. Most of the parents were completely unaware that they had the extra bit of chromosome 22 until they were tested after their child was found to have the extra bit.

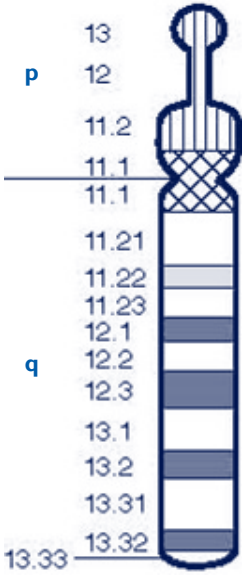
Anyone who has the extra bit of chromosome 22 has a 50 per cent chance of passing it on to any child of theirs. They have a 50 per cent chance of having a child without the duplication. This is true for each pregnancy.

It isn't possible to say in advance how mildly or severely a baby with the duplication will be affected - or whether they will be affected at all.

In most people with the duplication, the extra bit of chromosome 22 is the same bit that is missing in people with 22q11.2 deletion syndrome. This deletion syndrome is also called Shprintzen syndrome, velo-cardio-facial syndrome (VCFS) or DiGeorge syndrome.

Appendix

A gene that could be involved



Most of the 30-40 genes in the 3 Mb stretch of a 'typical' 22q11.2 microduplication have not been fully characterised. However, researchers believe that the absence of one particular gene, known as *TBX1* (19,744226-19,771116 (GRCh37/hg19)), is responsible for many of the typical symptoms of the 22q11.2 micro*deletion* syndrome, such as heart defects, cleft palate, distinctive facial features and hearing loss. They don't believe that it underlies any learning difficulties. 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 and it is suggested that when the gene is missing, as in a microdeletion or when there is an extra copy of it, as in the microduplication, normal development of organs can be disrupted. Having said this, many people with the microdeletion and the microduplication have no organ problems, suggesting that the *TBX1* gene contributes to problems but does not on its own cause them (Torres-Juan 2007; Zweier 2007; Ou 2008; Wentzel 2008).

What does that mean? Some possible genetic test results

46,XY,dup(22)(q11.2q11.2) This result shows that the expected number of chromosomes (46) were found in a male (XY rather than XX for a female). A duplication was found in chromosome 22, with two break points, both in the band known as 11.2. The extra material may lie directly beside the original location (known as 'in tandem'), or it may have been inserted somewhere else, such as on another chromosome, or further away on chromosome 22.

46,XX.ish 22q11.2(TUPLEx3) *de novo* This result shows that the expected number of chromosomes (46) were found in a female (XX rather than XY for a male). The test used a technology known as *in situ* hybridization (.ish), which showed that a marker known as TUPLE was present in three copies rather than two, as normally expected. *De novo* means that the parents' chromosomes have been checked and no duplication was found for the 22q11.2 region.

arr cgh 22q11.21(17,391,672-19,761,934)x3 hg19 This result shows that a technology known as array comparative genomic hybridization (arr cgh) revealed an extra copy (x3: remember that the normal copy number is two, one on each chromosome 22) of part of the band known as 22q11.21. The first extra base pair known to be present is 17,391,672 and the last extra base pair is 19,761,934. By taking the first number from the second, you can work out that there are 2,370,262 extra base pairs, or about 2.4 Mb of extra material. hg19 tells you which version of the human genome was used to make these measurements.

blood test showing normal chromosomes. The term that geneticists use for this is de novo (dn), meaning 'new'. De novo 22q11.2 duplications are caused by a change that occurred when the parents' sperm or egg cells formed, or possibly during the formation and copying of the early cells after the egg and sperm joined.

Whether the duplication is inherited or de novo, as a parent there is nothing you did to cause it and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary, workplace or lifestyle factors are known to cause 22q11.2 duplications. There is nothing that either parent did before or during pregnancy that caused the duplication, so no-one is to blame and there is no reason for anyone to feel guilty.

Can it happen again?

In families where both parents have been tested and one parent has the same 22q11.2 duplication as the child, each future pregnancy has a 50 per cent chance of having the same 22q11.2 duplication and a 50 per cent chance of having unaffected chromosomes. It's also possible, although rare, that a future pregnancy could have more than one copy of the 22q11.2 duplication. There is a case in the medical literature where a mother with the 22q11.2 duplication (so she has three copies of the 22q11.2 region) had a daughter with four copies of the 22q11.2 region, known as a triplication (Yobb 2005). Whether or not two additional copies of this region is clinically significant is unknown.

Because the 22q11.2 condition is so variable, it isn't possible to reliably predict the effects on the development, health and behaviour of the child.

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 22q11.2 microduplication or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 22q11.2 microduplication. This is called germline mosaicism and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the duplication.

Your genetics centre should be able to offer counselling before you have another pregnancy, you may also wish to read our guide 'Planning your next child.'

Will my child with a 22q11.2 microduplication have similarly affected children?

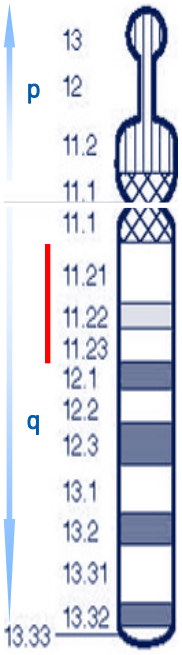
As an adult, your child with a 22q11.2 microduplication may well want to have children. We have not known about the condition for long enough to be certain if it affects fertility but it is very likely that fertility will be normal. In each pregnancy, someone with the duplication has a 50 per cent possibility of passing it on and a 50 per cent possibility of having a child without the duplication.

What is a 22q11.2 duplication?

A 22q11.2 duplication is a genetic variation in which there is an extra copy of a small piece of chromosome 22. The duplication is found near the middle of the chromosome at a place called q11.2. Because the extra bit is very tiny indeed, you will sometimes see it called a microduplication.

What we know about 22q11.2 duplications comes from studying people who have a reason for having a genetic test. The reason might be developmental delay, or a health problem, or perhaps the 22q11.2 duplication has been found in someone else in their family. This gives us a biased sample. If we looked for 22q11.2 duplications in the general population, we would have an unbiased sample, but it is very difficult to do. This means that at the moment we can't be sure about cause and effect with a 22q11.2 duplication. There is still a lot to learn, but this guide contains the best information we have to date.

The features of people with a 22q11.2 duplication vary extremely widely, even among members of the same family. People can have developmental delay, intellectual disability, slow growth leading to short stature, and weak muscle tone (hypotonia). Many people with the duplication have no apparent physical or learning difficulties or disabilities.



Chromosome 22

What does 22q11.2 duplication mean?

Chromosome 22 is one of the 23 pairs of chromosomes in the cells of the body that carry genetic material. The top bit down to the indent in the diagram on the left is known as p. The bottom bit is called q.

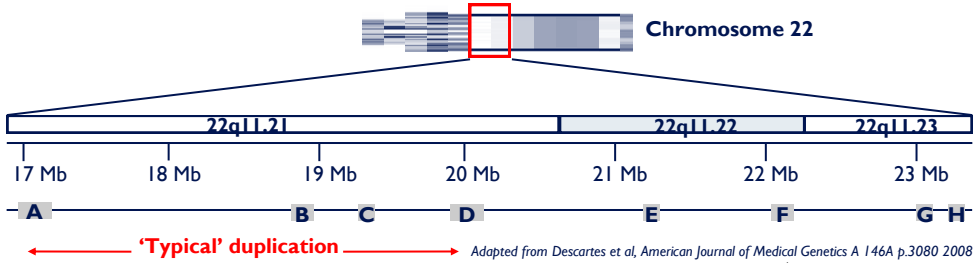
Chromosomes are made up of DNA, which contains the genetic instructions for development and functioning. DNA has a ladder-like structure, with the ladder's rungs formed from chemicals known as base pairs. The size of the tiny extra bit of 22q11.2 is measured in base pairs. There are millions of base pairs on a chromosome, so the numbers are usually shortened. One

Sources & references

The information in this guide is drawn from what has been published in the medical literature about babies, children and adults with a duplication of 22q11.2. 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 request most articles from *Unique*.

The guide also draws on information from *Unique*'s database. At the time of publication, *Unique* had 34 members with a 22q11.2 microduplication, and more than 110 people with 22q11.2 duplication were described in medical articles (Edelmann 1999; Ensenauer 2003; Beiraghi 2004; Hassed 2004; Lamb 2004; Somerville 2004; Portnoï 2005; Sparkes 2005; Yobb 2005; De la Rochebrochard 2006; Mukkades 2007; Courtens 2008; Laitenberger 2008; Ou 2008; Ramelli 2008; Wentzel 2008; Yu 2008; Clarke 2009; Portnoï 2009; Draaken 2010; Lundin 2010; Smith 2010; Liewluck 2011; Schramm 2011; Tan 2011; van Campenhout 2011; Agergaard 2012; Pebrel 2012; Pierguin 2012; Quelin 2012; Gong 2013; Kim 2013; Ribeiro 2013; Tucker 2013; Chen 2014; Cordovez 2014; Draaken 2014; Ghandi 2014; Pires 2014; Rees 2014; Warburton 2014; Campos 2015; Chang 2015; Grande 2015; Liu 2015; Zhang 2015).

million base pairs is called a megabase, and written as 1 Mb. Most people have a 22q11.2 duplication that is about 3 Mb in size. Typically, the extra bit starts around 17 Mb and ends around 20 Mb. Some people have smaller duplications, about 1.5 Mb in size. Some people have larger duplications, from 4 to 6 Mb.



Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

The references in this guide from the medical literature relate to these 'typical' duplications, unless we specify otherwise. Some people have an 'atypical' duplication of a slightly different part of 22q11.2. For more about atypical microduplications, *see pp 27-36.*

Looking at chromosome 22q11.2

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. One of these bands is band 22q11.2. A 22q11.2 duplication cannot be seen under a microscope. It can only be identified using new, more sensitive molecular techniques for analysing chromosomes. Your geneticist can give you information on the 22q11.2 duplication of your child. You can find more information in the appendix on page 39.

What's the difference between a 22q11.2 deletion and a 22q11.2 duplication?

Some people have a *missing* bit of 22q11.2, which is referred to as a 22q11.2 deletion. Names for the condition caused by having a 22q11.2 deletion include: del(22q11) syndrome, Shprintzen syndrome, velo-cardio-facial syndrome (VCFS), and DiGeorge syndrome. *Unique* has a separate guide to 22q11.2 deletions.

Do geneticists understand everything about the 22q11.2 duplication?

No, they don't yet. There are some big puzzles. One of them is why people in the same family with exactly the same duplication can be very differently affected. Another puzzle is why people with larger duplications are not necessarily more severely affected than people with smaller duplications. Both of these puzzles suggest that the rest of a person's genetic make-up is very important as well.

Are there people with a 22q11.2 duplication who have developed normally and have no speech, behaviour, learning or health difficulties?

Yes, there are, or at least we assume there are. The 22q11.2 duplication can be 'silent', or at least there may be no signs or symptoms that make a person stand out from the rest of their family. We know this because some parents, brothers and sisters of children with a 22q11.2 duplication have the same duplication, but do not have any obvious unusual features or delayed development - at least not to the point where they need medical or educational intervention. The effect of genetic conditions such as a 22q11.2 duplication on development, health and behaviour ranges from being barely perceptible to being obvious and severe. In this sense, they are like infections such as flu that can be mild or serious.

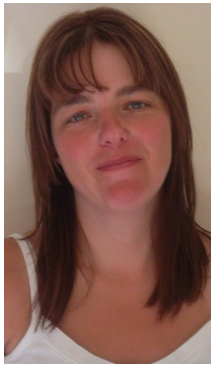
In your family, is the 22q11.2 duplication inherited or not?

About 70 per cent of people with a 22q11.2 duplication have inherited it from one of their parents. In some of these families, the duplication is also present in one of the grandparents, and possibly even further back. A Flemish study reports that 6 out of 10 children have inherited the duplication from one of their parents (van Campenhout 2011). In other families the duplication is an event that has occurred for the first time in the family. The genetic term for this is *de novo* (dn), which is Latin for 'new'. A new 22q11.2 duplication is an event that occurs when the sperm or egg cells are formed, or in the very earliest days after fertilisation. The only way to be certain is to check the chromosomes of both parents, even if they are themselves completely healthy. If one parent has the same duplication as the child, we can assume that it has been passed on from parent to child.

As a parent there is certainly nothing you did to give your child the 22q11.2 duplication and nothing you could have done to prevent it. No environmental, dietary, workplace or lifestyle factors are known to cause 22q11.2 duplications (or other chromosomal conditions, for that matter). There is nothing that either parent did before or during pregnancy that caused the duplication, so no one is to blame and there is no reason for anyone to feel guilty.

If one person in a family with the 22q11.2 microduplication is mildly affected, will others in the same family also be mildly affected?

Not necessarily. There is a lot of variation between different members of the same family who have the same duplication. We know that if one person is mildly affected, or not affected at all, others may be more severely and obviously affected. This variability includes differences in learning, health and behaviour problems. For example, it is quite common to find that a parent who has no learning difficulties has a child who needs extra support at school. It is also quite common to find different health problems in different members of the same family, all with the 22q11.2 duplication. You can see this variability among brothers, sisters and cousins with the duplication, as well as between generations - so between grandparents, parents and children. What is more, the Flemish study suggests that children who have a de novo duplication generally have better development and behaviour compared to children who inherited the duplication from one of their parents. Because only a small group of children was included a larger study is needed to confirm these results (van Campenhout 2011).



Mother and son: about 70% have the extra bit of chromosome 22 from one parent.

How do new 22q11.2 duplications occur?

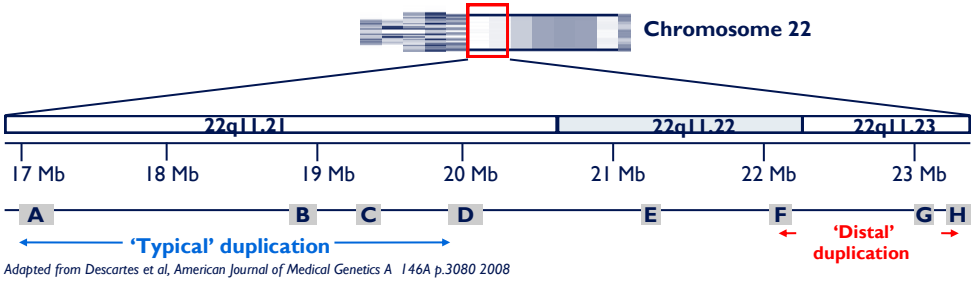
A blood test to check both parents' chromosomes is needed to find out why the 22q11.2 microduplication occurred. So far (see above), in about 70 per cent of all families described, a parent has passed the duplication on to the child. In the other cases, the duplication occurred when both parents had a

One child failed to thrive and had poor growth, which, with developmental delay, was the reason for her diagnosis.

Considering health, in one child, the tricuspid valve between the upper and lower chambers of the right side of the heart does not close properly, allowing blood to leak back into the upper heart chamber (atrium) when the lower chamber (ventricle) contracts. One child has a sacral dimple. Two children have tightly contracted joints. One has a spinal curvature (scoliosis).

Three children and two adults have an unusual head size: in one child and two adults, it was unusually large; in two others, unusually small. Two children had an unusually small lower jaw and chin (micrognathia) and one had an unusually large tongue.

Atypical microduplications at 22q11.2: 'distal' duplication (F-H)



Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

Twelve people have been reported in medical articles with this duplication of around 1.4Mb. However, information is only available for five of them: two 2-year-old boys, a boy of seven years, a boy of 8 years and a girl of 3 years. Three children inherited their duplication from their mother and three from their father (Coppinger 2009; Chang 2015).

Developmentally, the three boys in the Coppinger study are differently affected, although each one has low muscle tone: one has profound developmental delay; two have apraxia (inability to carry out skilled movements), one with dysarthria (problems articulating the sounds of speech) and one with a speech and language delay. The boy with profound delay has an unusually small head (microcephaly), while the boy with apraxia and speech delay has an enlarged head, with a build-up of fluid within the brain (hydrocephalus). The third boy, with apraxia and dysarthria, has a normal-sized head. He also has undescended testicles, which is the only medical condition noted for any of the three boys.

The 8 year old boy had developmental delay and some facial features including a low frontal hairline, deep-set eyes, a high nasal bridge, underdeveloped nostrils, a cleft lip and big front teeth. He has moderate intellectual disability and some behaviour issues (Ribeiro 2013).

The girl suffered from epilepsy from 6 months of age. An MRI showed pachygyria. She had microcephaly (small head), some unusual facial features like hypertelorism and a squint. She had severe developmental delay. She was not able to sit, roll over or talk. Also she had hypotonia and severe hearing problems (Chang 2015).

Is it possible to have other chromosome conditions as well as the 22q11.2 duplication?

This is entirely possible. When this guide was compiled, around one in seven of *Unique*'s members had another chromosome anomaly as well as the 22q11.2 duplication. Obviously, this situation complicates matters, because we cannot always be sure which chromosome anomaly is most responsible for the person's difficulties.

This child has a 22q11.2 duplication and an extra bit of chromosome 9. He has inherited both duplications from his parents.

This child has a 22q11.2 duplication and Gomez-Lopez-Hernandez syndrome, which causes baldness on the temples.

Does everyone with 22q11.2 duplication have the same extra bit of the chromosome?

No, they don't. Although most people with a 22q11.2 duplication have the 'typical' duplication, with an extra copy of about 3 Mb of genetic material in band q11.21, at least 12 other duplications of different parts of 22q11.2 are known about. *See pages 27-36 for information about 'atypical duplications'.*

22q11.2 is rich in genes. It's possible that having extra copies of these genes leads to some of the symptoms that people with the duplication experience. The typical 3 Mb duplicated part contains at least 47 genes. Little is known yet about what many of these genes do, but research is under way to determine which genes may contribute to the developmental delay and other problems that can affect people with a 22q11.2 duplication. *For more information on one of these genes, see page 39.*

You can discover the size and position of the 22q11.2 duplication in your family by asking the geneticist or by checking the base pair numbers on the laboratory report. You need to know this if you are going to read medical articles describing patients with a 22q11.2 duplication, because there can be very subtle differences in the size and place of the duplication on the chromosome, and this means that different genes are affected.

How common is it to have a 22q11.2 microduplication?

It's difficult to be certain how common 22q11.2 microduplications are. A study investigated the prevalence of 5 specific chromosome disorders including 22q11.2 duplications in newborns. This group represented the general population, because it was not known if the babies had health or developmental problems. The study suggests an estimated prevalence of 22q11.2 duplications of 1 in 1,140 persons in the general population (Tucker 2013). Many people with the duplication have no symptoms, so there is no reason why they would be diagnosed. People generally have a chromosome test because they or someone else in their family show signs of developmental delay or other concerns. Around 1 in 700 people tested for these reasons had the 'typical' or 'classic' 22q11.2 duplication in one study, and a similar number of people had a different 22q11.2 duplication (Ou 2008). A later study suggests a higher prevalence of 22q11.2 duplications in persons with developmental

problems (1 in 320) (van Campenhout 2012 Genereviews). Overall, well over 300 people with the 22q11.2 duplication have been reported in medical journals; when this guide was written *Unique* had 34 members with the duplication, and Chromosome22Central had 55 families and was aware of around 25 others. There must of course be many more people with the duplication than this; they just haven't been reported or aren't known to one of the support groups.

Is there a 22q11.2 duplication syndrome?

That depends on how you define 'syndrome'. Typically, geneticists define a syndrome as a group of characteristics that are common to all or most individuals with a particular genetic anomaly. However, that definition is changing now that we can detect very small chromosome differences, because the signs and symptoms are more variable, and less well-defined. So, by the 'old' criteria, we cannot yet say for sure that there is a specific 'syndrome' related to having a 22q11.2 duplication. However, the term is still commonly used in medical articles and by doctors to mean that the individual has the genetic difference.

The 'typical' or 'classic' 22q11.2 duplication

More than 300 babies, children or adults have either been reported in the medical literature or are known to *Unique* (Edelmann 1999; Ensenauer 2003; Beiraghi 2004; Hassed 2004; Lamb 2004; Somerville 2004; Portnoi 2005; Sparkes 2005; Yobb 2005; De La Rochebrochard 2006; Mukkades 2007; Courtens 2008; Laitenberger 2008; Ou 2008; Ramelli 2008; Wentzel 2008; Yu 2008; Clarke 2009; Draaken 2010; Lundin 2010; Schramm 2011; *Unique*).

Main features

- Differences in heart structure or function
- A problem with the roof of the mouth known as velopharyngeal insufficiency, with or without a cleft (split) in the palate
- Hearing loss
- Growth delay
- Developmental delay
- Need for support with learning
- Behaviour issues
- Some unusual facial features

2 years

Heart differences

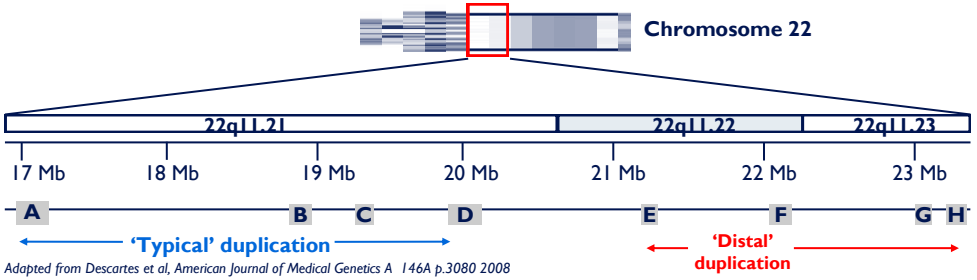
It seems that the great majority of babies with a 22q11.2 duplication are born with a structurally normal, healthy heart. But around 18 per cent (20/112) of those cases we know about have been identified as having differences in how the heart is formed, or how it functions. The problems are of different types and vary in severity: from small or mild defects that have little or no effect, and resolve naturally in time; to defects that require surgical correction; to complex, life-threatening anomalies.

The different heart problems seen so far include a slow heart rate; a ventricular septal defect; pulmonary stenosis; prolapse and insufficiency of the mitral valve;

delay was most obvious was in expressive speech and language, where he experienced a severe delay. Understanding was intact, however, and by four years he was communicating using speech. Since he is still so young, any learning difficulty is as yet unknown. At the age of four he can scribble, and write something like the first letter of his name. He has a statement to entitle him to learning support. As regards behaviour, at four years he is judged happy, friendly, and eager to please, with no behaviour on the autistic spectrum or other unusual or difficult behaviours. He has no sleep problems.

" He most enjoys playing superheroes, with cars and outside with his siblings. Friends and therapists say he is very compassionate for his age, sweet-natured and easy-going. I assumed the worst and while conditions can cause a change at any time, he has done pretty well. "

Atypical microduplications at 22q11.2: 'distal' duplication (E-H)



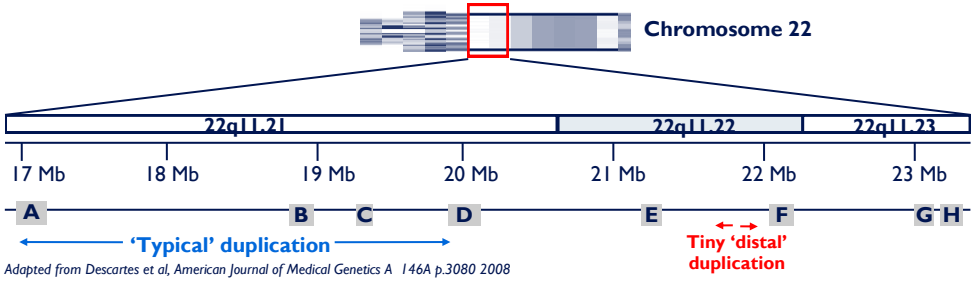
Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

Twenty-one people have been reported in medical articles with a duplication that extends for around 2.1 Mb. At least seven members of one family have this duplication and a further six parents were found to carry the duplication after their child was diagnosed. However, information has only been provided for a total of nine people (Descartes 2008; Coppinger 2009; Shimojima 2010).

Developmentally, everyone old enough to be tested shows some degree of delay. In two children it is mild, while in another, it is more significant. One child was operating at a 2-year-old level when she was 4½ years old and had severe speech delay. Another child had speech delay, not speaking until he was 20 months old, but with no delay in sitting or walking. One child was not talking or walking at 2 years, 9 months, and was considered to have a severe degree of delay. One child was too young for any developmental delay to be assessed. Two of the adults had learning difficulties and left school unable to read or write; both have children with learning difficulties. In their family, people with the duplication had learning difficulties and developmental delay, while those without the duplication did not. Another child has slight developmental delay at nine years, but has a diagnosis of attention deficit hyperactivity disorder, and another child is hyperactive. Two have been diagnosed with low muscle tone, in one case profound.

Two children have epilepsy. One child developed partial seizures when asleep at the age of 2 years, 8 months and epileptic spasms when awake, and was treated with anti-epilepsy drugs.

Atypical microduplications at 22q11.2: tiny 'distal' duplication (between E & F)



Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

A 4-year-old boy is a member of *Unique*. His duplication is a small one, between 0.15 Mb and 1.7 Mb, between base pairs 21,769,300-21,919,500. The small size of this duplication makes it very unlikely indeed that it is the cause of his problems. So the description that follows is included just for the sake of completeness. The first signs of any condition were a failure to thrive from the age of five months, missing gross motor milestones and only being able to turn his head to one side. Following a normal birth at 38 weeks, he had a normal birth weight of 6lb 4oz (2.8 kg) and was 19" (48 cm) long. He was mildly hypotonic but his breathing was normal and he left hospital after two days, needing no special care. He was successfully breastfed, although the low muscle tone in the mouth and face led to dribbling. At the age of four, he eats a normal diet.

Healthwise, he has generally done well. His heart, spine, genito-urinary system and kidneys all proved to be normal, and he had no serious respiratory infections or other illnesses as a baby or toddler. However, he was diagnosed with hypothyroidism, for which he takes replacement therapy. Further, he developed a 'mild seizure disorder' at 19 months. By four years, he is being weaned off his anti-epilepsy medicine. He has also had frequent ear infections and has tubes in the ear drums to improve his hearing.

In terms of growth, he has not grown as fast as a typical child of his age. From five months, his growth rate slowed until he was in the lowest three per cent of the population for height and weight, and at four years he is short and underweight.

He has a few unusual physical features, including skin webbing between two of his toes and flat feet, for which he wears corrective inserts in his shoes. The soft spot on top of his head (fontanelle) was unusually large and slow to close. Facially, he has some subtly unusual features, including a slight droop of the left upper eyelid and he has very fair skin and hair.

Developmentally, he seemed to progress normally to five months and then stop. A slight delay was first noticed in reaching his physical (gross motor) milestones, and he benefited from physical therapy. He rolled and sat only slightly later than expected, but at his first birthday, the tone in his arms was still either too floppy or too taut and he had difficulty staying on his hands and knees. Nonetheless, he was commando crawling by 15 months and walking by 16 months. By this age, his muscle strength seemed to be normal. By the age of four, he was walking and running without any aids or supports. He was toilet-trained by four years. The area in which

persistent ductus arteriosus; coarctation of the aorta; atrial septal defect or patent foramen ovale; and a 'boot' shaped heart. These terms and phrases are explained on this page and page 8.

The more complex heart problems include a multiple anomaly with a single upper collecting chamber, transposed blood vessels and a hole between the lower chambers; transposition of the great arteries with Ebstein's anomaly and a ventricular septal defect; tetralogy of Fallot; and hypoplastic left heart, in one case with an interrupted aortic arch. These terms and phrases are also explained on this page and page 8.

Additionally, in one case known to *Unique*, an adult in their 40s was diagnosed with a valve problem and will probably need a replacement valve within 10 years. As valve problems are common in the general population, this finding may or may not have anything to do with the 22q11.2 duplication (Ensenauer 2003; Hassed 2004; Somerville 2004; Sparkes 2005; Yobb 2005; De La Rochebrochard 2006; Mukaddes 2007; Laitenberger 2008; Yu 2008; *Unique*).

Heart terms

Atrial septal defect (ASD): A hole 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.

Boot shaped heart: A characteristic sign of tetralogy of Fallot on X-ray (*see page 8*).

Coarctation of the aorta: The aorta that takes the blood from the heart to the rest of the body is narrowed. This forces the left side of the heart to pump harder to push blood through the narrowing. Treatment is tailored to the individual child, but if necessary the narrowed section can be surgically removed or made larger.

Ebstein's anomaly: A defect affecting the right side of the heart. The tricuspid valve that controls blood flow from the top chamber (atrium) to the bottom (ventricle) is too low down. This makes the top chamber too big and the bottom chamber too small. The valve may also be leaky, letting blood that should be in the ventricle leak back into the atrium.

Hypoplastic left heart: The left side of the heart has not developed properly and is very small. The aorta, the artery that takes blood from the heart to around the body, is tiny, and blood can only reach it through the ductus arteriosus: a blood vessel that normally closes within days of birth. Although babies seem healthy at birth, within days they become very ill and will need heart surgery.

Interrupted aortic arch: Part of the aorta, taking blood from the heart to the body, is missing. This leads to severe obstruction to blood flow in the lower part of the body.

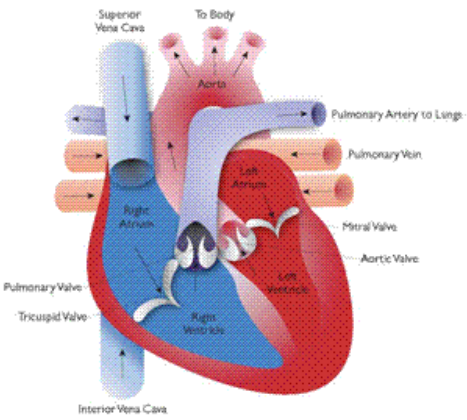
Mitral valve prolapse and insufficiency: The mitral valve between the upper left heart chamber and the lower left chamber does not close well enough to prevent back flow of blood when the ventricle contracts. The

7 years

flaps of the mitral valve allow blood from the left ventricle to flow back into the left atrium.

Patent foramen ovale: An opening between the two upper chambers of the heart does not close in the first year of life, as expected. When it remains open, this allows extra blood to pass from the left to the right side of the heart.

Persistent ductus arteriosus: This is a channel between the aorta and the pulmonary artery that takes blood to the lungs, which usually closes shortly after birth. When it stays open, the lungs receive more blood than they should, and the heart has to work too hard. It can be closed using minimally invasive surgery, by inserting a coil via an artery in the thigh. Tissue grows around the coil, closing the gap.



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.

Tetralogy of Fallot: A complex heart condition involving both a ventricular septal defect (VSD) and an obstruction just below the pulmonary valve, that decreases the normal flow of blood, with the aorta shifted to the right so that it sits astride the VSD. 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. Children with tetralogy of Fallot will need a surgical operation. 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.

Transposition of the great arteries: The vessels taking blood away from the heart are on the wrong side: the aorta arises from the right, and the pulmonary artery from the left ventricle. For correction an arterial switch operation is usually performed very soon after birth.

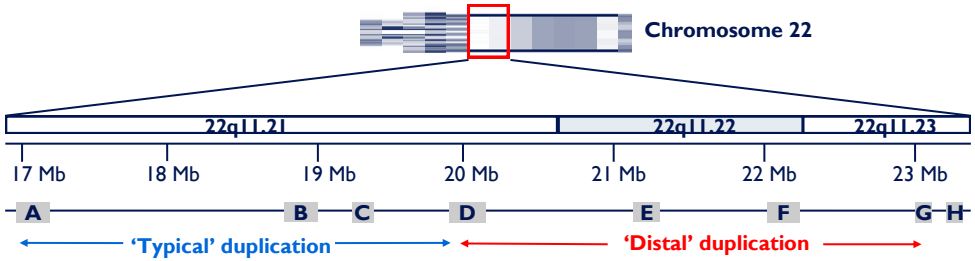
Ventricular septal defect (VSD): A hole in the wall between the two pumping chambers of the heart (ventricles) allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Specific treatment for VSD is determined individually. A baby with a VSD will be evaluated periodically. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from exposure to extra blood flow.

Cleft palate (split in the roof of the mouth)

Most babies with a 22q11.2 microduplication are born with a normally formed, intact roof of the mouth. Around one baby in five (22/112), however, has something unusual about the shape or structure of their palate. The roof may have a high arch, there may be a split in the front hard part or in the rear soft section of the palate, or the tissue that hangs down from the palate at the back of the mouth may be divided (bifid uvula). These unusual shapes and structures can add significantly to any feeding

spine, and a developmental defect of one eye. He also had small, tapering fingers and toes (Coppinger 2009).

Atypical microduplications at 22q11.2: 'distal' duplication (D-G)

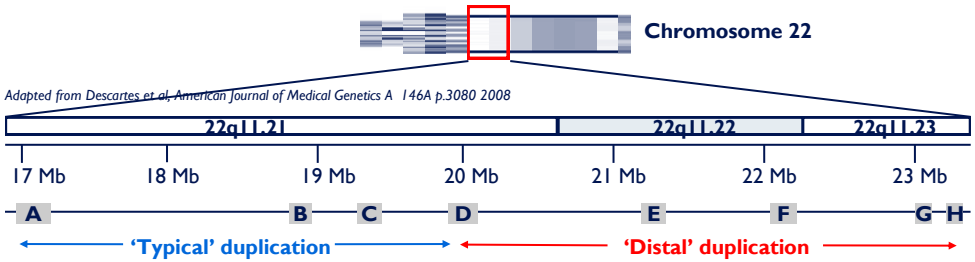


Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

Two people have been reported in a medical article with a duplication of around 3 Mb, overlapping the duplication described on page 33, but extending further along the chromosome.

There is some medical information about one of the two: a 12-year-old girl with severely delayed development. As well as having an unusually small head (microcephaly), a heart defect (a ventricular septal defect: a hole between the two lower pumping chambers), a spinal curvature needing a brace, low muscle tone and possible seizures, she was not able to talk or to walk, and moved around in a wheelchair. She had tightly contracted joints and a number of other minor anomalies, such as webbed fingers and toes (Coppinger 2009).

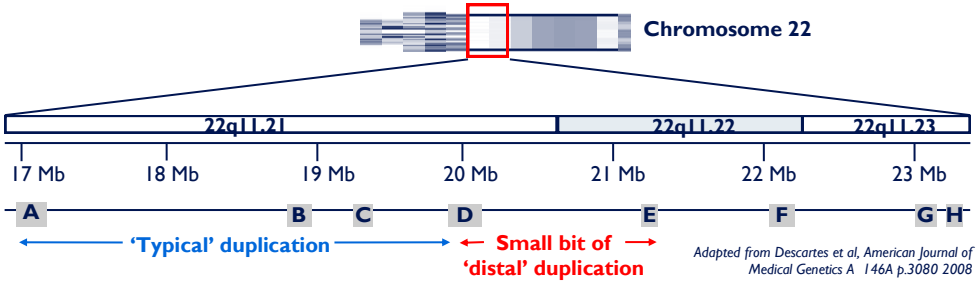
Atypical microduplications at 22q11.2: large 'distal' duplication (D-H)



A mother and son have been reported in a medical article with duplications of around 3.6 Mb, overlapping the duplication described above, but extending further along the chromosome. The boy, 6 years, 9 months old, has possible seizures but is otherwise healthy, and has no developmental delay or low muscle tone. However, he has marked behaviour difficulties (Coppinger 2009).

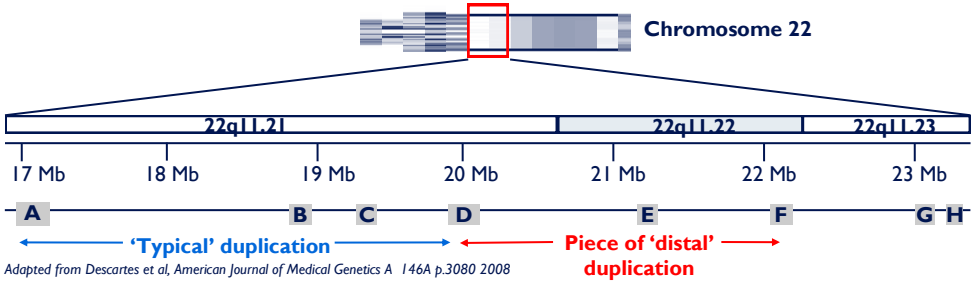
A father and daughter with a duplication of 5.6 Mb are described in a second article (Tan 2011). The girl had tetralogy of Fallot, reflux of urine from the bladder into the kidneys with caused damage to the kidneys, hearing loss, speech delay and some non-specific facial features. Her growth was above average. She had some anxiety problems when she was 7. Her father had no intellectual disability. As a child he had speech therapy because of language delay.

Small bit of 'distal' duplication (D-E)



Two people have been described in a medical article: a 28-month-old girl whose father had the same duplication of around 1.1 Mb. While the father has no apparent learning difficulties and needed no support with his learning, his daughter had a degree of developmental delay. She was able to sit at an appropriate age (seven months) but was only able to walk when she was almost two years old, and by the age of 28 months was using only a few single words. As well as hooded eyelids, a feature she shared with her father, the girl had tiny holes in front of her ears (preauricular pits) and a range of subtly unusual facial features. She also had a squint (strabismus) and large pads at her fingertips. Otherwise she was healthy (Ou 2008).

Atypical microduplications at 22q11.2: piece of 'distal' duplication (D-F)



Three people have been reported in medical articles with duplications of around 2 Mb overlapping the duplication described on pages 32-33, but extending further along the chromosome. There is some medical information about two of the three: one a newborn baby boy, the other a toddler.

The baby boy was born with a range of quite serious health problems, including a bridge of skin or tissue blocking off the anus (imperforate anus), a markedly small left kidney with a duplicate collecting system and kidney reflux, and heart anomalies (a persistent ductus arteriosus, a patent foramen ovale and an unusual artery supplying blood to the right arm). (*For explanations, see pages 7-8*). One testicle was small. His left thumb had an extra joint, like a finger. His toe nails were tiny and underdeveloped. He may possibly have had a spinal curvature. We don't have any information on how he developed after the newborn period (Ou 2008).

A toddler aged 20 months by contrast had no heart, kidney or genital problems, but had tight, contracted joints, dimples along the lower spine and at the bottom of the

difficulties a baby may have, making feeding with a special teat such as a Haberman feeder necessary. Depending on the extent and position of the cleft, surgical repair may be needed (Ensenauer 2003; Hassed 2004; Portnoï 2005; Yobb 2005; Mukaddes 2007; Laitenberger 2008; Wentzel 2008; *Unique*).

" No cleft (split) in the palate, but a high palate. I think it's affected her feeding, but her issues could also be due to low tone and lack of coordination of her suck-swallow-breathe pattern. We used a Haberman mini-feeder for some time. She still receives speech therapy. "

Velopharyngeal insufficiency

Around 70 per cent of people with a 22q11.2 micro*deletion* have a palate problem known as velopharyngeal insufficiency (VPI). VPI is a disorder that results in the soft palate at the back of the mouth closing incorrectly, allowing air to escape through the nose instead of the mouth. VPI can be a structural problem (short palate), a functional problem (hypotonia of the soft palate muscles) or a combination of the two. People with VPI have difficulty pronouncing most consonants correctly, including *p, b, g, t* or *d,* and may substitute unusual speech sounds or a glottal stop. Their speech may also sound nasal, as if they have a chronically stuffy nose. After detailed investigations, VPI is usually treated with speech therapy, and sometimes with surgery or with a speech appliance called an obdurator.

VPI is especially common among children with a cleft palate and has been found in around 15 per cent of children and adults with a 22q11.2 micro*duplication*. Of *Unique*'s 34 members with the typical 22q11.2 microduplication, one has been diagnosed with VPI (3 per cent), compared with 16 in the medical literature (20.5 per cent) (Edelmann 1999; Ensenauer 2003; Hassed 2004; Portnoï 2005; Ou 2008; Wentzel 2008; *Unique*).

Hearing loss

While most babies, children and adults with a 22q11.2 microduplication have normal hearing, a significant number have some hearing loss. It is very common to have a type of temporary hearing loss that is caused by a build-up of fluid inside the ear spaces (glue ear, or chronic otitis media), and this is very common in toddlers and young children regardless. Even though glue ear usually resolves naturally in time, it is often treated by inserting tubes into the child's ear drums to improve their hearing at an age that is important for speech development.

A permanent, sensorineural hearing loss appears to be much less common, but can occur. One *Unique* member was being considered for cochlear implants when this guide was compiled. Overall, around one child or adult in three (32/112) has some degree of hearing loss (Ensenauer 2003; Somerville 2004; Yobb 2005; Portnoï 2005; Mukaddes 2007; Courtens 2008; Ou 2008; Lundin 2010; *Unique*).

Growth

It seems that the majority of babies with a 22q11.2 duplication grow at the expected rate before birth and are born around the expected weight and length for gestation. Among babies surveyed by *Unique* and in the medical literature, the average birth weight at term was 3.2kg (7lb 2oz), with a range of 2.3kg (5lb) to 4kg (9lb).

There appears to be no consistent effect on body build, with some children described

as slight and underweight, others frankly overweight, and the majority being appropriate for age and family background. After birth, the growth rate may slow down in some babies and children with the duplication. Some are diagnosed with failure to thrive, which simply means that they are not gaining weight at the expected rate, regardless of food intake. Around one child in 10 is unusually tall (Beiraghi 2004; Hassed 2004; Lamb 2004; Portnoï 2005; Yobb 2005; De La Rochebrochard 2006; Courtens 2008; Ou 2008; Ramelli 2008; Clarke 2009; Wentzel 2008; van Campenhout 2011; Unique).

Development

Having a 22q11.2 microduplication may increase the likelihood of developmental delay, but does not necessarily cause it. Many children and adults with the duplication have never experienced a significant delay in any area of their development. Overall, one person in three reported in the medical literature or known to *Unique* has experienced no developmental delay; typically these are people who were only diagnosed because a family member, usually their own child or sibling, was diagnosed first. Two people in three have experienced some delay, which may be most obvious in behaviour, responding to others, learning to move, concentrating, learning to talk or all of these areas. However, it is possible that there are more people with a 22q11.2 microduplication who have experienced no delay and never come to the attention of doctors.

Developmental delay in children with the 22q11.2 duplication is typically mild-to-moderate and responds well to early intervention and therapy. However, the severity of delay cannot be predicted from the diagnosis and some people are more or less noticeably affected. Even within the same family, the degree of delay, if any, can be highly variable.

Families say:

" The iPad is quite helpful with cause and effect and fine motor skills. " *21 months*

" Follow a definite routine and don't rush your child. " *9 years*

Sitting, moving, walking (gross motor skills)

In children who do experience some developmental delay, a delay in being able to roll over, sit, become mobile and walk is common. A few children with developmental delay reach these gross motor skill milestones at the expected age, but most children are a little late. Within *Unique*, babies with the 22q11.2 microduplication learned to roll over between five and 18 months (average eight months); they sat up between six and 12 months (average nine months); they became mobile, usually by crawling but in some cases by bottom-shuffling or bunny-hopping, between seven months and 2 years, 7 months (average 14 months); and they were up and walking between 12 months and 2 years, 8 months (average 19 months). One child reported in the medical literature started to walk at three years. Two children of 3½ and 4 years, 10 months were not walking yet. Mobile children went on to climb stairs between the ages of 17 months and three years (average 2 years, 3 months) (Mukaddes 2007; *Unique*).

A Flemish study including 11 children with developmental delay reports a variation in the delay. Some children (2/11) had very mild developmental delay and others a

of four, she was developmentally at the level of a 2-year-old, and attended a school for the medically disabled with all-day learning support. Overall, when she was four years old, her level of learning difficulty was judged to be mild. Despite an early start - she smiled at a couple of months, was babbling by four months and said her first word at six months - her speech and language were especially delayed: at the age of three, she was using both speech and signing to communicate and was able to create 3-word sentences and phrases. She was toilet-trained day and night by three years and by four years is pretty independent in personal care. She tries to dress herself, but sometimes needs help. She goes to the bathroom on her own and is able to wash her hands.

In terms of behaviour, this girl is described as outgoing, 'sweet and gentle when she wants but can be stubborn and aggressive towards her siblings'. She has a short concentration span, and lots of tantrums. She occasionally wakes, saying she is scared, but then falls asleep again easily.

In health terms, one baby was born with a cleft lip (a split in the upper lip) and two had a cleft palate (a split in the roof of the mouth, needing surgical repair). One baby was underweight at birth (2.268 kg/5lb) and had breathing difficulties, with noisy breathing caused in part by soft, limp structures in the nose and throat, and apnoea spells when she would stop breathing, as well as seizures as a newborn baby. After birth, she stayed in hospital for three weeks and needed extra oxygen and a feeding tube. She had reflux, where feeds readily return up the food passage, and was at risk of inhaling part of the feeds (aspiration). Her seizures persisted despite anti-epilepsy medicine and still affect her at four years. There have been at least 20 episodes in four years where she stopped breathing and she has twice needed resuscitation. She has also had a large number of other health problems: at three months, she developed fibromyalgia, causing long-term pain. She had incorrectly developed hip joints and her heart has an unusual 'boot' shape. By the age of three, she had been admitted to hospital more than 20 times. At the age of four, she was taking seven regular medicines, including anti-epilepsy drugs, medicines for asthma, anti-allergy medicines and vitamin B6. With repeated hearing loss, she had twice had tubes inserted to improve her hearing.

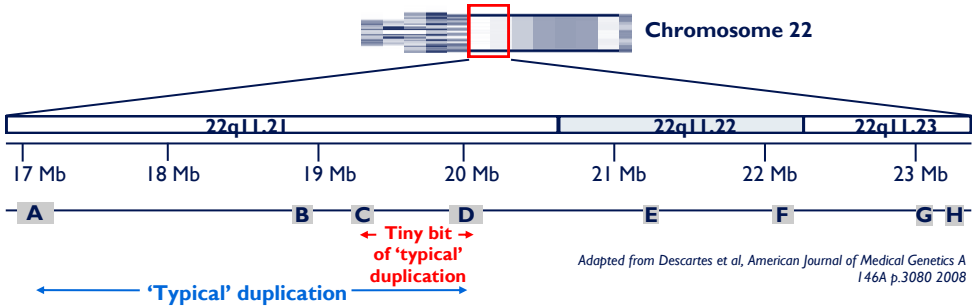
" Aside from everything, she is pretty bright and figures out electronics easily. She loves to play outside, to color, and to make friends. She loves watching kid movies, listening to music, and the toys she loves are blocks, puzzles, and dolls. She is a joy to my family as she helps us see things differently. It has been a hard, long road for her, but with the support of myself and my husband she is going to be fine. It is not easy to care for a sick child who looks somewhat normal but has medical issues. People are cruel and stare and talk, and we as their parents need to be their voice and advocate at all times. I am blessed to be her mommy. "

Atypical distal microduplications at 22q11.2 (between D and H)

The following descriptions are of people who have a duplication next to, but not overlapping with, the more common 3 Mb duplication. These are also referred to as 'distal' duplications, because they are farther down the length of the chromosome. Because the duplicated regions do not overlap, they do not contain the same genes, and therefore should not be expected to have similar presentations. They are included here for completeness only.

2012. This boy was examined because of hypotonia, developmental delay and serious asthma. He was able to sit at 12 months and was walking independently at 22 months. He was able to talk single words when 3 years of age. He had mild facial features including a large front head, folds on the inside of the eyelids, long lashes, a broad nose bridge with nostrils turned outwards, ears that were tilted backwards and with pits, a small mouth with a high palate and a high hairline. He had no genital problems. He had inherited the duplication from his mother. She had a nasal voice and dyslexia, but no other features (Pebrel 2012).

Other 22q11.2 microduplications: tiny bit of 'typical' duplication (C-D)



Three families have been described: two reported in medical articles, and one at *Unique.* Of the 12 people known about, eight seem unaffected by the duplication and only know about it because they were tested after a relative was found to have it. In one family, a baby, his mother, two aunts, uncle and grandfather have the same small duplication. In the second family, the father passed the duplication on to his child, who had developmental delay. In the third family, two children, their mother and her father have the duplication. In this family, a small duplication of the short arm of chromosome 9 has also been passed down over three generations and one of the children with the 22q11.2 duplication has the family 9p duplication as well. Since the second chromosome anomaly could affect this child, details are not included here. The 22q11.2 duplication in all three families includes part of the region covered by the 'typical' 3 Mb duplication but is much smaller, around 0.4-0.5 Mb in size (Fan 2007; Fernández 2009; *Unique*).

Regarding the effects of this small duplication on development, the literature is biased by the fact that testing to identify the duplication was done precisely because of developmental problems. So it's impossible to say at this point whether this very small duplication has any effect on development and behaviour. With this in mind, the following information is available on the few reported children with this duplication.

A baby of 13½ months was developing normally and his five relatives with the duplication were also apparently unaffected. However, two other children did have developmental delay although their parents and grandparents, also with the duplication, did not. One of these two babies started to roll, sit and walk at the expected age, crawling at nine months, walking on her own by 18 months and climbing stairs by 20 months. However, she did need supports to stabilise her feet. Her delay first became obvious when speech did not emerge as expected. By the age

moderate delay (8/11, for example they learned to walk after the age of 18 months). One child, a boy, had severe developmental delay. His development came to a halt at the age of 3. A decline in development was noticed at the age of 6. At the age of 7 the boy had the development of a child of 15 months. All children had some difficulties with movement. Three had mild problems concerning fine motor skills and the others had difficulty with gross motor skills (van Campenhout 2011).

Low muscle tone (hypotonia), making children feel floppy, is common as are loose, mobile joints, which mean that children have to work harder to become mobile. Two *Unique* families specifically mentioned weakness and low tone around the shoulders. One child had hip dysplasia, where the ball and socket hip joints have not developed perfectly and may need splinting, immobilisation or surgery. One boy had contractures of the joints of the arms and legs (Liewluck 2011). His duplication starts a bit earlier on the chromosome compared to the typical duplication and is a bit smaller than usual.

Families said that conventional therapies were the most useful in getting their children mobile: early intervention, physiotherapy and occupational therapy.

" Daphne is not crawling or walking. Since she is only 10.5 kg (23lb), we carry her or use a stroller. We are currently in the beginning stages of acquiring a wheelchair, for when she goes into the school system. She has a stander, and she uses a gait trainer at daycare. She also has AFOs (ankle foot orthoses: a type of support). She enjoys swimming, playing in the bath, and being outdoors. She does seem to like rough play such as spinning or being tossed in the air. " *21 months*

" Dario walks cautiously, most enjoys throwing balls and rough play. The physical therapist has helped a lot with walking straight rather than wobbling, and his feet are positioned forward when stepping on stairs. " *3 years*

" Gabriella has a special stroller. She doesn't do many physical activities at the moment due to unsteadiness and tremors. Before, she used to like slides, swings, and throwing a ball. " *3 years*

" Aiden is an independent walker and most of the time he's running. Mobility isn't much of a problem now. He can do most everything other kids can do, but he's slower than his peers, especially when it comes to climbing. He can't do things like monkey bars or pedalling a bike without help because his muscles aren't strong enough. He loves to play at the playground, go fishing, go for hikes, etc. He's very into anything with high activity. " *4 years*

" Kendra dragged her left side to walk at one point, but now walks better. She still has feet problems, and complains of pain when walking due to fibromyalgia. She used AFOs (ankle foot orthoses: supports). Early intervention was the most useful therapy. " *4 years*

" Skye doesn't walk, but walks on her knees. She uses a kid walker, a standing frame, leg wraps, a block trolley and special boots to try and stop her from pointing her toes. " *4 years, 10 months*

" Sophie walks without aids or supports, and enjoys throwing and kicking balls, riding bikes and scooters, and running. " *5 years*

" Edward has very poor coordination. He has a large ball to sit on at home, and at school a chair with sides and a footplate, and a wobble sensory cushion. He most enjoys swimming, running around outside, and swings. His low tone means that he

2 years

5 years

9 years

Almost
13 years

likes to lie down or 'loll' a lot. " *9 years*

" Joshua moves normally but can be clumsy. His favourite activities are cricket, swimming and football. He loves all sports, and swims in the advanced group and attends galas with the Special Olympians disability group. He was a gold medallist in the national postal swim. "

" Joshua plays football with the Community Sports Foundation for children with disabilities and was a mentor on a Playing for Success scheme, helping other younger children explore different ways of learning. He has been to para-games in Manchester and is due to go to London. There are a handful of people who have made his life easier and allowed him to thrive and learn to achieve, even with the huge amount of difficulties he has had to overcome. " *13 years*

Using their hands (fine motor skills)

While some children are able to use their hands with no problems at all, the possible combination of developmental delay, low muscle tone and loose joints means that others are typically slow to use their hands purposefully and to coordinate hand use with eye use. One child in three known to *Unique* has been diagnosed with dyspraxia, where the way the child organises movements is impaired or immature. As a result, babies will be late to play with toys and to hold, drop and pick up objects and later on will find holding a mark-maker more difficult. They will also be late to learn to self-feed. They will benefit from occupational therapy as well as play therapy.

" Daphne does not use a pincer grasp yet. She is just now beginning to pick up foods to bring them to her mouth, using a whole-hand grasp. " *21 months*

" Dario cannot feed himself properly yet, and still needs help with a spoon. He cannot yet drink from a regular cup. " *3 years*

" Gabriella previously had average fine motor skills, but in the past few months has developed tremors. " *3 years*

" Aiden used to press very hard with writing tools when he was colouring and more recently I've been told he doesn't press hard enough when doing his letters. He doesn't seem to have a hard time holding objects. He can hold a pencil correctly, but he has a hard time writing his letters and it takes him over an hour to write the alphabet. He also has a very difficult time using scissors to cut, and buttoning clothing. " *4 years*

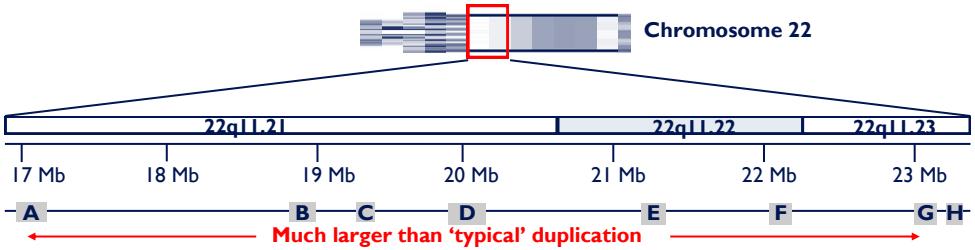
" Skye has constant hand movements but she is able to pick up most objects; she is unable to feed herself with a spoon, but can pick up some finger foods. She is unable to draw or write yet. " *4 years, 10 months*

" Sophie still grips a pencil with her fist. Her drawing is still squiggles. " *5 years*

All four have needed support with their learning and the son, aged 13, has a moderate learning disability. He has poor coordination and was also slow to sit and start moving, as were possibly his mother and one of his sisters, but not the other.

The older members of this family do have some behaviour and psychiatric problems, but the younger girls of eight and 10 are so far unaffected. The 13-year-old son is considered aggressive as well as possibly depressed and anxious, while his mother is diagnosed with depression and anxiety.

Other 22q11.2 microduplications: much larger than 'typical' duplication (A-G)

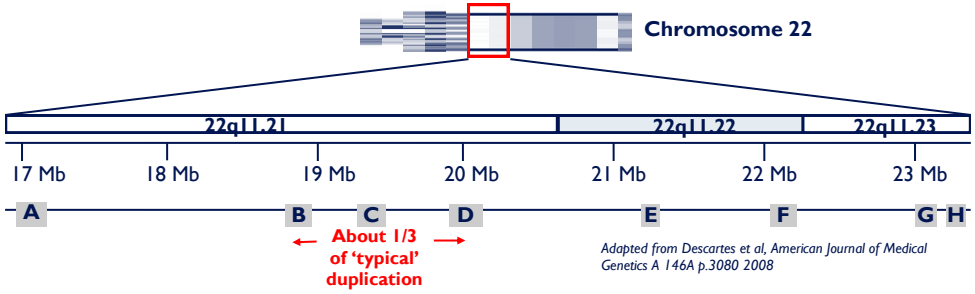


Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

Two girls have been reported in a medical article, both eight years old when diagnosed. They are unrelated. Each has a 22q11.2 duplication that is about 6 Mb big: it is twice the size of the 'typical' duplication, starting at the same point in 22q11.21 but extending twice as far (Ensenauer 2003).

Although both girls need support with their learning, they have quite different health and other issues. One has VPI (*see page 9*) and attention deficit. The other girl has hearing difficulties; a stenosis (narrowing, blockage) of the urethra, the tube that drains urine from the bladder; incorrect rotation of the intestines; long sight and/or astigmatism; seizures; and she is in the bottom 10 per cent of the population for height or weight. She was slow to sit, crawl and walk, and has a mild-to-moderate degree of learning difficulty.

Other 22q11.2 microduplications: about one-third of 'typical' duplication (B-D)



Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

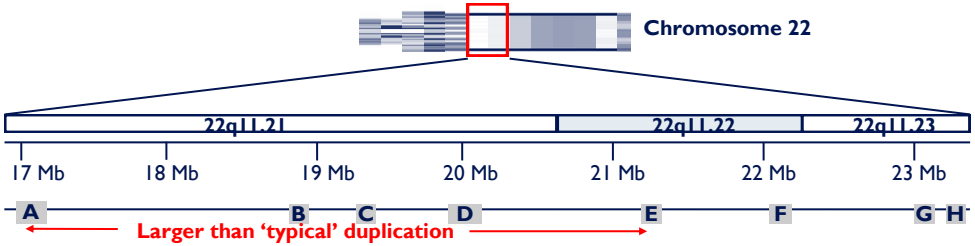
A father and 2-month-old baby have been reported in a medical article. They have a small 22q11.2 duplication that extends for about 1 Mb and includes around one third of the 'typical' 3 Mb duplication at 22q11.2. The father has no development or health problems that we know of. The baby, a boy, was born with ambiguous genitals (Ou 2008). A 3 year old boy with a similar duplication has been reported in an article of

All of the five children were under the age of five when they were described, so we only have limited information on their development. One was developing normally at two months; one had developmental delay and needed learning support by 2½ years. Of the three who were late to start talking, one also had a mild degree of developmental delay and one was hyperactive at the age of four.

They had different health problems but were overall quite healthy. Two siblings failed to thrive: that is, they failed to gain weight and grow at the expected rate. Their father, also with the duplication, is short in stature. Growth was normal in other children. One child had repeated ear infections (very common in all small children) and a squint (strabismus), but was otherwise healthy. Two were born with very noisy breathing and one of them was diagnosed with laryngomalacia, where the structural framework of the voice box is soft and limp. This baby also had small cysts in the brain of a type (subependymal) that are quite common and generally held not to be significant.

A 3-year-old had an enlarged spleen, but no serious illness.

Other 22q11.2 microduplications: larger than 'typical' duplication (A-E)



Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

Four people have been reported in a medical article. They are all from the same family, aged between eight and 31 years at diagnosis: a mother, her son and two daughters. Each has a 22q11.2 duplication that is about 4 Mb big: that is, it starts at the same point as the 'typical' duplication but extends about 1 Mb further along the chromosome and includes more genes. The mother's father is also known to have carried the duplication (Ensenauer 2003).

These four members of the same family have quite different issues, although there are some areas of overlap. Of the four, one daughter had poor growth, one daughter has a cleft palate (a split in the roof of the mouth) and she and possibly her mother have a condition known as velopharyngeal insufficiency (VPI), where the air spaces at the back of the throat do not close completely, allowing air to escape through the nose. VPI is caused by a cleft or short palate, hypotonia of the velopharyngeal muscles or a combination of the two. It is particularly common in people with a 22q11.2 *deletion*. Both mother and son are unusually long sighted. Both have a kidney anomaly, corrected in the mother when she was eight. The son has mild hydronephrosis, an enlargement of the right kidney, and a number of other unusual health problems: he underwent an accelerated puberty, has headaches, unusually long sight and the two bones in his forearms are believed to be fused (radioulnar synostosis). His head is unusually small (microcephaly), and his left upper eyelid drooped markedly (ptosis) and was surgically lifted when he was five.

" Edward used his hands to eat until he was four and still has poor fine motor skills " *9 years*
" Allison has weak hands and tires easily when having to write a lot " *12 years*
" Joshua hates writing and will do anything to avoid it. He can use a knife and fork, though previously he was very messy. He has a laptop but typing is difficult too, as he is clumsy when tired " *13 years*

Families recommend: Try to have children feed themselves as much as possible.

Personal care

The difficulties with fine motor skills mean that many children will be late to learn how to undress, dress, and wash themselves. Toilet training is also frequently delayed and in some children significantly so.

" Daphne is completely dependent right now. She will 'help' when putting on clothes, by pushing her arms out through the sleeves - the right arm more than the left " *21 months*
" Dario can take off his shoes, socks, and pants and wash his hands. He is not yet toilet trained " *3 years*
" Gabriella doesn't like water but can wash herself, brush her teeth (she likes to), can help put on some clothing, but is not potty trained " *3 years*
" Kayleigh tries to help with dressing: she can remove her trousers, shoes, socks, and coat. She will wash in the bath and clean with wipes. She is not yet toilet trained " *4 years*
" Kendra is pretty independent. She tries to dress herself, sometimes needing help. She goes to the bathroom on her own and is able to wash her hands. She was toilet trained day and night at three " *4 years*
" For Aiden, potty training is a problem. We had him almost completely potty trained and then he regressed. After that he was urine trained (not stool though) and he regressed several times, first at three, and then again at age four, but now he's regressed a little and no longer stays dry all day any more. He can put on his own clothes, but it takes him a long time to do it. He tries to wash himself, but he still needs some help. He has an issue with getting water on his face, so he doesn't wash his own hair. He can use the toilet by himself, pull his pants up and down, etc. He cannot wipe himself yet and isn't stool trained at this time. He's fearful of being alone in the bathroom and will not use the toilet without someone else present " *4 years, 8 months*
" Sophie is in pull-ups at night time after previously doing well, but now going back to wetting and soiling. She needs help getting dressed and putting on shoes " *5 years*
" Edward needed help with personal care until he was five or six years old. Today he still struggles with socks and shoes and cannot do laces. He was toilet trained in the day at 4½, but not yet at night " *9 years*
" Totally independent for personal care; she was toilet trained at 18 months " *12 years*
" Joshua can cope well with personal care as long as a routine is followed. He has to have his hair done, his clothes chosen and laid out. He still wets the bed some nights, but has much improved " *13 years*

Learning

A baby born with a 22q11.2 microduplication may be more likely to need learning support than a baby without the duplication. However, many adults and children have the duplication without experiencing any learning difficulty or disability. Some children and adults with the duplication are above-average learners and university graduates. A Flemish study shows that 4 out of 11 children have nearly normal intelligence. Three are in regular schools with support (for example because of hearing problems). Six children attend a special school for children with intellectual disability (van Campenhout 2011).

3 years

Although more than 100 people are known about already, this is still too few to know whether there is a distinctive type of learning difficulty linked to the duplication. We do know that the range of learning difficulty is very broad. At one end are children who need a small amount of extra help in a mainstream school but go on to lead normal, productive working lives. At the other end of the scale are people with a severe learning disability. This makes it impossible to predict an individual child's learning ability in advance. Even members of the same family, all with the 22q11.2 microduplication, have very different learning profiles.

Within *Unique*, more members have a learning difficulty than are reported in the medical literature. Bear this in mind when you read families' experiences below.

" Gabriella is around a 24-month level. She likes hands-on activities like puzzles, and can draw a circular figure " *3 years*

" Dario is at the level of a child of 18 months. He likes music and recognises songs. He isn't reading yet, but can scribble " *3 years*

" Kayleigh has a moderate learning difficulty. Her memory is quite good; she loves books and points and names things in them. She can draw a face and circle and write K for Kayleigh. She attends a mainstream nursery where she will complete a further year, and her statement entitles her to 15 hours support, which is full attendance " *4 years*

" Kendra has mild learning difficulties. She does very well learning about electronics and figures them out easily. She draws smiley faces and attends a school for the medically disabled, where all day the teachers work with her " *4 years*

" Aiden is ahead of his age at school, at a 5-6 year level. He has an excellent memory and is very good at drawing things: people with many parts, places, animals (he especially likes drawing bugs), action scenes, etc. He can write some letters legibly, though some days his name looks good and other days it's illegible. He can't read many words on his own yet and isn't into books very much, but he likes me to read books to him on occasion. He attends a typical classroom at our local state-funded Head Start preschool. The only thing he receives at school is an educational consultant. They watch him to see if he's developing well or falling behind " *4 years, 8 months*

" Sophie is significantly behind her peers at the moment. She has a very good memory for routines such as the school day and will also remember upsetting times, such as going back to an appointment which has upset her. She cannot read yet,

" No respiratory infections that needed hospital treatment, but has had multiple pneumonia and bronchitis. " *21 months*

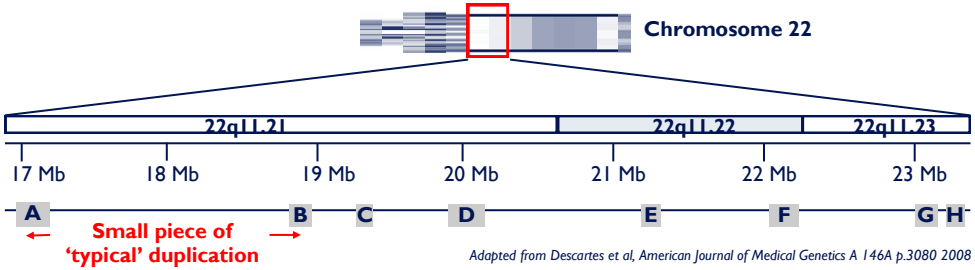
" He has had bad chest infections and five hospital admissions for asthma. When he was five, he was shown to have suboptimal immunity to the immunisations he had at birth, so he was reimmunised and immunised against pneumococcal infections, which have really helped with his upper respiratory and chest problems. These are improving with age: he still has frequent colds and has had five courses of steroids, but is generally much healthier and has had no hospitalisations. " *9 years*

Breathing

The great majority of babies, children and adults with a 22q11.2 duplication breathe normally and are able to keep the oxygen levels in the blood at a normal level. Around five per cent of individuals, chiefly children, have spells when they stop breathing while asleep (sleep apnoea) and one adult has mechanical help with breathing at night. In one child the apnoea spells seemed to coincide with growth spurts.

Two children have significantly floppy airways: in one, the nose is affected; in the other the structural framework of the larynx (the voicebox) was soft and limp, causing noisy breathing and needing surgical correction at four months (Edelmann 1999; Hassed 2004; Portnoï 2005; *Unique*).

Other 22q11.2 microduplications: small piece of 'typical' duplication (A-B)



Adapted from Descartes et al, American Journal of Medical Genetics A 146A p.3080 2008

Seven people in three families have been reported in medical articles. Each of these people has a small piece around half the size of a 'typical' 22q11.2 duplication. The piece is around 1.5 Mb in size, and starts at around 17 Mb, finishing at around 18.6 Mb (Alberti 2007; Ou 2008; Yu 2008). Although it is unclear whether this duplication is the cause of their condition, their descriptions are included for completeness.

People with this very small duplication seem to be affected in very different ways. The adults did not know they had a 22q11.2 duplication until their chromosomes were tested after they had a child with the duplication. One functions as an entirely normal member of her society. One man had special education as a child, and like his children, was late to start talking and has a nasal tone of voice. He is healthy, a heart murmur having resolved naturally. He is short, and has an unusually small head (microcephaly). He also has a few minor unusual features which don't affect him, most of which he shares with his children: extra nipples, a split in the small piece of fleshy tissue that hangs down at the back of the roof of the mouth (bifid uvula); a single crease across the palms of his hands; and squared finger tips.

oesophagus) (De La Rochebrochard 2006); one had a missing 12th rib (Portnoï 2005); one, no spleen and a T cell (immune cell) deficiency (Ensenauer 2003); one was born with no thyroid gland and needed treatment with thyroid hormone; in one baby the thyroid was partly absent. In another the thyroid was not present, this child had a 22q11 duplication but also another chromosomal disorder (Courtens 2008; Thorwarth 2010; Kim 2013); and one had an unspecified gastrointestinal abnormality (Yobb 2005).

General wellbeing

Overall, children and adults with a 22q11.2 duplication are generally healthy. A minority of young children have frequent respiratory infections (*see below*) and an even smaller number (three children and one adult that we know of) have significant allergies. A further small number, around six per cent, have frequent bad headaches or migraines (Clarke 2009; *Unique*). Overall, a small number of children go to hospital more often than typically developing children and one child had had more than 20 hospital stays by the age of three. The most common reason for going to hospital is to have ear tubes placed, but respiratory infections are another common reason.

Healthy: 8 years

Two babies had pyloric stenosis, where the passage between the stomach and the small intestine narrows so that feeds cannot get through, causing forceful vomiting in young babies and requiring surgical correction. One child gets frequent staphylococcal infections and queries have been raised about the strength of the immune system in two other children. One baby was diagnosed with fibromyalgia at three months and is monitored by rheumatology. One adult man was found to have a thyroid nodule, and needed treatment with thyroid hormone. One adult man had Sturge Weber syndrome, a disorder in which you are born with a port wine stain and neurological problems including learning disabilities, seizures and one-sided paralysis or weakness, as well as other potential problems. One boy was diagnosed with a low level of calcium (Courtens 2008; Ou 2008; Yu 2008; *Unique*).

" His general health and wellbeing is great. He has had no hospital stays and takes no regular medications. " *3½ years*

" He gets coughs and colds all year round, and takes a long time to recover. " *5 years*

" If he misses a dose of loratadine (anti-allergy medicine), he becomes wheezy and starts to cough the next day. " *13 years*

" Overall, a healthy young woman. " *adult*

" Her health is not great: she has low energy and frequent stomach issues. " *adult*

Respiratory infections

Most children and adults with a 22q11.2 duplication have normal airways and breathing and have no more coughs, colds or chest infections than other typically developing children. However, a small number have had frequent, serious chest infections and have had immunisation against pneumococcal infection. At least one baby's frequent chest infections reduced significantly when he was put on reflux medication and his feeds thickened. There are 4/99 diagnosed with asthma, and one takes asthma medications but breathing tests suggest that he does not have asthma.

At least two children have had their tonsils removed and one, the adenoids as well. One adult has had two corrective surgeries to the sinus passages (Yu 2008; *Unique*).

write or draw specific shapes. With a statement she attends a mainstream school with full time 1:1 support. " *5 years*

" On paper, Edward's level of difficulty is severe, but we would say it is moderate. He is currently achieving the higher levels of the preparatory stages for accessing the UK national curriculum. His relative strengths are in maths and information and communication technology; he can do number bonds to 20. However, he has very poor reading skills, but knows the letter sounds, reads letters and some familiar words. His drawing and writing skills are roughly at a 4-year level: he draws people and animals and writes single words (his name, mummy, daddy etc) like a 4-year-old. He has an excellent memory, especially for people and places. He loves and understands maps and can find his way around a complex, unfamiliar environment, like the zoo. Edward has had a statement since he was three and attends an integrated school for mainstream and special children with 100 per cent 1:1 learning support. " *9 years*

" Allison has many different learning problems, a neuroprocessing disorder and a diagnosis of dyslexia. Her long and short term memory are good. She is reading grade 3-4 books in grade 7 and attends a public school with a statement that entitles her to help within the general classroom and assistive technology. " *12 years*

" Joshua has difficulties with speech and memory and problems with visual and auditory perception. Socially he is doing very well and has many friends, so he has remained in mainstream school, but he has especial problems in reading, writing and communicating. Memory is a problem: he has significant delay in recalling facts: recall can be up to two weeks later. Questions make him extremely stressed. He loves numbers but has severe difficulties learning basic literacy skills. He learned to read and write in his ninth year, and at 13 can write or draw but it is such a problem, he will only do the bare minimum and will cause a fuss to try not to do it. "

" Joshua's current statement entitles him to 15 hours support but he receives 25 hours. His current assessment grades him as 3C on the English system for general cognitive ability, but lower for reading and spelling. " *13 years*

" Susan had learning difficulties as a child, with special teaching in inclusive classrooms. She had difficulties with reading, writing and no understanding of math. Her highest qualifications are 11th grade, ie age 16/17. " *adult*

" He attended a mainstream secondary school but had an individual education plan and needed help with reading and writing. He attained no post-school qualifications and works as a storeman in a tile factory. " *adult*

" Paula was a slow learner at school and had difficulty reading and spelling as a child. When she spelt her name, she got confused and jumbled the letters. She sat the Higher School Certificate in an adapted version especially for children in her class. " *adult*

What helps children to learn?

3 years - Does best with individual attention. Wish to please is helpful.
4 years - Striving to please people.
4 years - Determination. The Signalong signing system.
4 years - Lots of patience and repetition.
5 years - The special needs coordinator at her school has liaised with a special school, who said that the way they teach Down's children is a good way for someone

like her to learn.
9 years - Success helps him to learn: he likes it when he does well. He has to be in the mood as he is very stubborn. Learns best kinaesthetically, using touch or sight instead of verbally.
12 years - 1:1 teaching.
13 years - Likes to please and will respond well if he will get a house point in school; now used for a list of his goals. He has always responded well to having a 1:1 helper and using a reward system.

Speech

Speech and language develop in the normal way in some babies and children with a 22q11.2 microduplication. In others, the failure of speech to emerge as expected is an important early warning sign of an underlying condition. In some children, the speech delay is the only sign of delay; in others, there are delays in other areas. In a significant proportion of *Unique* members, speech and language was the most delayed area of development.

Communication milestones were generally delayed among *Unique* members: babies first smiled on average at four months (range six weeks to nine months); they first babbled on average at 12 months (range 4-24 months); and they said their first words around 17 months (range among those already speaking 4-30 months).

Speech production difficulties are common among *Unique* members with a 22q11.2 microduplication, but only one child had been diagnosed with VPI (*see page 10*). While nasal speech has been noted in the medical literature, this was not found in the *Unique* membership. Unusually, the parents of children with a 22q11.2 microduplication almost all believed that speech therapy had been extremely useful in helping their child to communicate.

" Daphne mostly uses vocal noises. I think she understands things: occasionally she will give a 'high five', and gets excited when you say it's bath time, etc. She says *mama*, but I don't think she associates a meaning with it yet. She has no expressive language right now. " *21 months*

" Dario has no speech, so we use picture cards to communicate with him. He uses gestures, some sign language, and vocal grunts. He cannot form words properly due to his cleft but understands more than he can express, and gets frustrated if we don't give him what he wants or starts smiling when he gets what he asks for. " *3 years*

9 years

" Gabriella has mild delay in receptive language and moderate expressive delay. Recently she has started regressing with some reception and is having some recall issues. She uses voice, gesture, and some signs to communicate, as well as phrases - usually 1-3 words but occasionally up to 4-5 words. " *3 years*

" Bailey has only started saying a few words, approximately at the level of a 2-year-old. He usually says a single word that gives some indication of what he wants or he points. He mostly uses single words such

" I don't think she can see distances well. I think that affects her motivation to be ambulatory. She wears glasses for near-sightedness but we won't know how well she can see until she can respond verbally to a functional eye exam, so we cannot develop strategies to manage her vision issues until that time. " *21 months*

" Ptosis: eye drops every week to dilate the bigger eye so he's forced to use the droopy eyelid. " *3 years*

Teeth

In *Unique*'s experience, children with a chromosome disorder generally have a higher rate of dental problems than typically-developing children. This may be due to a number of problems: unusual dental development; unusual size of the jaws, leading to overcrowding or widely spaced teeth; feeding difficulties and delayed eating and chewing activity; and tooth grinding, wearing down the enamel. Teeth may emerge late and milk teeth may be late to fall out. Extra teeth may be found and either milk or adult teeth may be missing.

The unusual combination of potential problems means that children and adults with a 22q11.2 microduplication may need sensitive and specialist dental care. Among 16 children and adults, six have some special feature affecting their teeth (*Unique*).

" She is tube fed and has oral aversions, so it's hard to brush her teeth. " *21 months*

" His teeth are misshapen, generally small, and different sizes and colours. He still has an extra baby tooth and the X-ray shows no adult tooth underneath. His baby teeth have been slow to fall out; so far he has only lost seven. " *9 years*

" She has already had six teeth removed but needs three more removed. " *adult*

Body

The great majority of babies with a 22q11.2 duplication are born healthy, with no specific conditions affecting any of their organs. A number of unusual conditions have nonetheless been found. There is, however, no pattern to these: some are normal developmental variants and others may have no link at all with the 22q11.2 duplication.

Based on reports of 93 children with 22q11.2 microduplications, seven have been reported to have some anomaly of the kidneys and/or lower urinary tract. The anomalies noted included: an extrarenal pelvis (a normal developmental variant where the collecting system is located outside the kidney) and the bladder was slightly distended; blockage at the ureteropelvic junction (the area that connects part of the kidney to one of the tubes that carry urine to the bladder), which caused an enlarged left kidney, the removal of some damaged areas of kidney and high blood pressure; enlargement of part of one kidney; a duplicated right kidney; a small kidney (renal hypoplasia); and hydronephrosis, where the kidneys become enlarged due to urine being unable to drain properly from them (Hassed 2004; Courtens 2008; Schramm 2011; *Unique*).

Four out of 93 have bladder exstrophy, where the skin on the lower abdomen has not formed properly, leaving the bladder exposed on the outside of the abdomen (Draaken 2010; Lundin 2010; Pierquin 2012; Draaken 2014). One baby was born with their internal chest and abdominal organs on the opposite side of the body to normal (De La Rochebrochard 2006); one needed surgery at 11 months to correct a hiatus hernia (protrusion of the stomach into the chest cavity through the hole for the

has abnormal development of the lower end of the spine, known as caudal regression syndrome with two vertebrae fused together; and another has two fused vertebrae in the neck area. One baby was born with a sacral pit, a small hole at the end of the spine. If the dimple is shallow and the end can be seen, and is in the crease between the buttocks, it is not usually a sign of any underlying problem. All the same, poo from a dirty nappy can lodge inside, so it is important to keep it clean and cover it well with barrier cream. An ultrasound scan can show whether the pit is deep or connects with the spinal canal (Ensenauer 2003; Courtens 2008; Clarke 2009; Lundin 2010; Schramm 2011).

Anomalies in the genital area

Generally speaking, babies with a chromosome condition are more likely to have a genital anomaly than babies with typical chromosomes. This is especially obvious among boys. Around 20 per cent of baby boys (11/52) with a 22q11.2 microduplication have something unusual about the genitals but there is no consistent pattern to the anomalies observed. The anomalies include: hidden penis, requiring corrective surgery (scrotoplasty); hypospadias, where the hole normally at the end of the penis is on the underside instead, in one case with a downward curve of the penis known as chordee; undescended testicles; a blockage in the urethra, the tube leading out from the bladder through the penis; and an inguinal hernia, caused by the failure of the hole that allows the testes to descend into the scrotum during fetal life to close properly. One young man also had a narrowing of the anus, with a channel between the prostate gland and the rectum (Ensenauer 2003; Beiraghi 2004; Lamb 2004; Portnoï 2005; Schramm 2011; Kim 2013; *Unique*).

Eyesight

Babies and children with a chromosome disorder or developmental delay usually have a careful eye examination to ensure that any problem with vision is addressed early, thus maximising their potential for development. Among 97 children and adults, a number have droopy eyelids (ptosis), which is significant when it covers the pupil of the eye. Seven have a squint (strabismus): treatment depends on the cause but can include patching the stronger eye, eye movement exercises, glasses to correct a refractive error such as long sight, and surgery to realign the muscles that hold the eye in place. Three children have nystagmus: a jerky movement of the eyes that can be caused by a problem with the eye or the visual pathway from the eye to the brain; although it cannot be cured, there are several treatments that can help. Nine children and one adult have either short or, more commonly, long sight, correctable with glasses if the child will wear them. One child has pupils that do not react to light and wears sunglasses outdoors. One child has a developmental eye defect affecting her vision, known as a chorioretinal coloboma. An adult had a 'rope-like' growth removed from the front of her eye. A further adult has unspecified poor vision in one eye. One child had ptosis and Marcus Gunn jaw winking (the upper eyelid moves up when opening the mouth). This child also had abnormalities of the eye movements and the blood vessels in the retina. Another child had glaucoma, retinal detachment in both eyes and cataract in the left eye. An eye examination in a girl showed folds and scar tissue in her macula (Ensenauer 2003; Yobb 2005; Mukaddes 2007; Courtens 2008; Laitenberger 2008; Ou 2008; Cordovez 2012; Ghandi 2014; *Unique*).

as *mum, hi, bye, nan, sissy, bottle, ham* and *cheese*. He is able to understand simple instructions and has no problems with the sounds of speech and no VPI. " *3 years, 6 months*

" Kayleigh's biggest difficulty was her speech. At three, she had around 10 spoken words but tended to use non-verbal communication as a first option. Her understanding was excellent. Now, she uses speech, usually 2-3 word phrases, but occasionally also sign language. However, her speech is not always clear and she has difficulty saying certain sounds, such as *g* and *t* as in *butter*. She does not, however, have a diagnosis of velopharyngeal insufficiency. " *4 years*

" Kendra is very delayed in speech and language but is now using 3-word sentences as well as sign language. She first smiled at a couple of months of age; first babbled at four months; her first word at six months was *dada*. Sometimes she just talks, even if she does not know what is going on. She replaces lots of letters with an *s*. " *4 years*

" Aiden's speech is delayed, especially his receptive language, but his conversation is fluent. He also has articulation problems and velopharyngeal insufficiency. " *4 years, 8 months*

" Skye is unable to talk but can express her needs: when she is hungry, she usually goes into the kitchen and hangs around, or watches you eat. When she is tired, she will usually fall asleep where she is or start to become whiney. She has some understanding: if you ask her for a cuddle she will place her head on your shoulder. " *4 years, 10 months*

" Sophie's speech is delayed by two to 2½ years. She can use some words and uses 2 -3 word phrases but will point to things if she can't say them. She has difficulty with the *th* sound and substitutes *d*. " *5 years*

" Edward's speech and language skills used to be poor but he can now speak quite well. His receptive language is far better than his expressive language. He is still unclear and has difficulty with *s, f, th* and *sh* sounds, but some days the content is good and other days there is just lots of babbling. He has just started to ask simple questions such as 'What you doing?' " *9 years*

" Allison used to struggle with communication and speech. Her speech is now fluent but can be disjointed due to her word order. She has total understanding but has been diagnosed with an auditory processing disorder as well as apraxia, and she has difficulties with some sounds of speech, although no diagnosis of VPI. " *12 years*

" Joshua talks in one-word replies but uses 2-3 words if needed. He has a good understanding of language but some speech production difficulties " *13 years*

" Speech difficulties with word order, vocabulary and articulation. " *adult*

Behaviour

It is not yet known whether any particular behaviour is associated with having a 22q11.2 microduplication. The evidence from *Unique* suggests that children are usually highly sociable. Where problems occur, they most commonly involve activity levels (overactive, hyperactive); temper control and aggression; and concentration. A small number of children have been diagnosed with autism and more are believed to have autistic traits, such as a tight adherence to routine. Other problems include immaturity, anxiety, and poor impulse control. If behaviour management programmes do not work, medication has often been tried, generally with success.

Methylphenidate is the medication used most often.

In the medical literature, there are a number of reports of children with a 22q11.2 microduplication and unusual behaviour. These only affect a small minority, although one researcher (Wentzel 2008) found a behaviour disorder in half of all the published reports. The disorders included autism (Hassed 2004; Mukkades 2007; Ramelli 2008); obsessive-compulsive disorder, and Tourette syndrome: a condition that causes people to make repeated movements or sounds called tics (Clarke 2009). Other researchers have found aggression and poor impulse control in 7/67, including a father and two sons (Ensenauer 2003; Yobb 2005; Courtens 2008; Yu 2008); hyperactivity with/without difficulties with attention in 20/78(Ensenauer 2003; Beiraghi 2004; Somerville 2004; Ou 2008; Ramelli 2008; van Campenhout 2011); psychiatric disorders including depression and anxiety in 3/78(Ensenauer 2003; Beiraghi 2004; Yobb 2005; Wentzel 2008; van Campenhout 2011) and unspecified problems in six further adults and children (Portnoi 2005; Ou 2008; Yu 2008). Sleep problems were reported in 3 out of 11 children in a Flemish study (van Campenhout 2011).

In 2014 a large study was performed investigating chromosome disorders in persons with or without schizophrenia. This study suggests that the 22q11.2 duplications were significantly less common in the group with a diagnosis of schizophrenia compared to the control group. Thus this duplication may protect against the development of schizophrenia (Rees 2014).

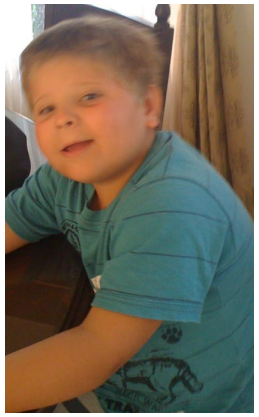
" Daphne is very happy and easy-going. If she has a bad day, it is usually due to some physical issue such as constipation or an ear infection. Socially, she prefers her parents over other people. She does quite well now when other people want to hold her although she often doesn't respond when people speak to her: I'm not sure if it's due to her vision issues, or delays. She has gotten a lot better with other kids, thanks to daycare, and is no longer intimidated by busy, noisy environments. There is a boy in her class at daycare who likes to snuggle her. If she doesn't want him to, she looks around for an adult and says *Ahhh.*" *21 months*

" Dario is very happy and willing to explore; very social with adults, more than children. " *3 years*

" Gabriella is mostly happy and pleasant, but does have major rages where she is violent. These happen out of the blue, usually for no known reason. She wants me to hold her all the time, and has definite separation anxiety. She also has hallucinations. Socially, she will sometimes smile and shake hands and other times will scream and is scared when people talk to her. " *3 years*

" Kayleigh is a very happy and loving child. She shows signs of ADHD and is constantly on the go. She can act shy to begin with but is very sociable. She does have some autistic features: she likes things in order, such as the same toys in her cot, play kitchen, books, and dolls. " *4 years*

" Kendra likes things her way, so we have lots of tantrums. She is sweet and gentle when she wants, but can be aggressive towards her siblings and at times is stubborn.



8 years

Head and brain

Some people with a 22q11.2 microduplication have a small head, some large, and most average. The head is usually a normal shape, but occasionally it has an unusual shape. In a Flemish study 3 out of 11 children had a large head and 5 had a small head (van Campenhout 2011). One reason for a baby's head being flat at the back is a delay in gross motor skills, so that the baby lies flat on its back for longer periods than a typically-developing baby, at an age when the bones of the skull are still soft enough to be moulded by the position the baby adopts. Another reason for an unusual shape to the head is early fusion of one or more of the seams between the bony plates of the skull (craniosynostosis) (Ou 2008; *Unique*).

When the structure of the brains of people with a 22q11.2 microduplication is investigated, it is usually found to be normal. There are occasional unusual findings, but there is no recognisable pattern to these. The unusual findings include: arachnoid cyst (two cases): a collection of spinal fluid between two of the three membranes that cover the brain and spine; in one child the arachnoid cyst was found together with other slight changes in the architecture of the brain, that were hard to interpret; delayed myelination (one case): a delay in the natural developmental process in which nerve fibres are covered in a protected sheath; non-specific abnormalities in parts of the white matter in the brain (one case); polymicrogyria - an excessive number of small, partly fused, convolutions on the surface of the brain (Courtens 2008; Quelin 2012; *Unique*).

Epilepsy

Twelve youngsters have been diagnosed with epilepsy or an abnormal electrical activity in the brain and five babies had staring/vacant spells or fits, but were not diagnosed with epilepsy. Two children had convulsions brought on by fever. The fits or vacant/staring episodes first arose between the neonatal period and four years of age. Medication controlled seizures in some children, but not in others. Two families have noticed an arrest or regression in their child's development after the emergence of seizures that was not eliminated by anti-epileptic drug treatment. Seizures, not fully controlled with medication, caused one child to drag the left side of her body (Edelmann 1999; Ensenauer 2003; Lamb 2004; Yobb 2005; Mukaddes 2007; Wentzel 2008; *Unique*).

Spine

Four children and adults have been diagnosed with a spinal curvature (scoliosis), requiring monitoring or, in more severe cases, bracing or surgery. One adult has a hidden form of spina bifida, which is usually an incidental finding on an X-ray; one

Can you tell?

In each of the brother/sister pictures on the left, just one child has a 22q11.2 duplication. Can you tell which one?

Answer below

In both pictures, the child on the right has the 22q11.2 duplication.

Some children have difficulties with fine motor skills, so are later to feed themselves and do better with adapted cutlery (Portnoï 2005; Wentzel 2008; *Unique*).

6 months

" Daphne would not latch on and was not successful at taking a bottle. I pumped breastmilk for 13 months. A gastrostomy tube was placed at six weeks as a condition for taking her home. Today, she is still primarily tube fed but will drink water from a straw, and is starting to take bites of crunchy foods, such as potato chips, and will eat some stage 3 baby foods. We have a variety of spoons that she uses. She learned to drink using a Honey Bear straw cup. " *21 months*

" Gabriella had swallowing problems. Puréed food would get stuck in the back of her throat and we used juice to wash it down. Today she is on solid foods but eats very little. " *3 years*

" Bailey has a sensory problem with and around his mouth. He was unable to eat any food until he was about three years old and was on a special formula. He can now eat most soft food, but only in very small amounts, and is still on the special formula. " *3 years, 6 months*

" Bottle fed. Unable to eat solid foods, all foods had to be puréed. She can now eat everything as long as it is soft " *4 years, 10 months*

" As a baby, Edward couldn't latch on to the breast or suck well and was given a bottle. Today he has an excellent appetite, loves most foods except sweets, jelly, and summer fruits and loves to chew and eat raw vegetables. " *9 years*

" As a baby, Joshua cried all the time and was a very unhappy baby and toddler. For some years now he has only eaten plain foods such as pasta, bread, and cereals. He currently drinks a pint of water with a meal. He needs to sit in the same seat at the table and gets upset if it is different. " *13 years*

Facial

While many children and adults with a 22q11.2 microduplication simply look like other members of their family, others have some unusual facial features. Overall, there doesn't appear to be a pattern, so individuals with a 22q11.2 microduplication don't look especially like each other. One researcher found that the most common unusual features were widely spaced eyes (70%), a broad flat nose (53%), a small lower jaw and chin (52%), unusually formed ears (45%), skinfolds across the inner corners of the eyes (epicanthal folds, 42%), and downslanting eyes (41%) (Wentzel 2008). A less common but distinctive feature is tiny holes or else skin tags in front of the ears, observed in at least 10 per cent of people with the microduplication (Edelmann 1999; Portnoï 2005; Yobb 2005; Ou 2008; Yu 2008; *Unique*).

Kendra has asthma and epilepsy and her medications make her tired or hyperactive at times. She has a short concentration span and sometimes says impolite things without thinking. " *4 years*

" Aiden is usually very good when we are out. It's an odd occasion that he has a public meltdown. At home he tends to have more problems: tormenting his little brother by holding him under blankets or sitting on him, not toileting as well, tantruming, acting less dependent. He is restless compared with his peers, has a lowered sense of dangerous situations and tends to dart away from us. He's very social and interacts well with other people, though sometimes he still violates boundaries. He's very friendly with adults and doesn't seem to appreciate 'stranger danger'. He has a behavioral therapist and therapeutic staff support who come six hours a week to help him manage his behaviour. " *4 years, 8 months*

" Skye is an extremely happy girl, always smiling and laughing. She gets excited when she knows that she has done something that you are pleased with. A very social little girl, happy to go to anyone. " *4 years, 10 months*

" Sophie often has tantrums and needs constant supervision as she has no sense of danger. She finds it hard to socialise with other children, and can be very challenging when tired or upset as she will scream or throw things. " *5 years*

" Edward has complex behaviours: he has stopped biting his wrists but can still be aggressive and not aware of own strength. He is very friendly and will still cuddle or kiss anyone. Socially, he is great with adults until he has had enough, when he wants to be on his own. He is less good with children but likes playing with them for a limited time. He has behaviour support organised by the hospital. " *9 years*

" Allison is a very sweet and kind-hearted child. Her behaviour is good and age-appropriate. She interacts well socially, but doesn't always understand social cues. " *12 years*

" Joshua looks like other children of his age but is more immature and mirrors the behaviour of the age group he is with. Socially he manages extremely well without having to say much. He displays unusual behaviours at times such as attachments to certain cuddly toys, hand flapping, chewing and a blankness at times, and was obsessed with vacuum cleaners as a child - although his specialists do not think he is autistic. We are currently waiting for an assessment of attention deficit hyperactivity disorder (ADHD). He chatters constantly, especially when he's relaxed, and is fidgety all the time. He has to be active. This became obvious once he was taking melatonin and sleeping through the night. He is also argumentative, always thinking he is right. He has mood swings: definite ups and downs which follow a 3-monthly cycle. He also has visual, perceptual and auditory difficulties and scores on the first centile for visual perception. A sensory profile is currently under way." *13 years*

" She has many emotional problems and although a great parent, struggles with the day-to-day aspects of life. She needs things in a certain routine or order, finds change very hard, and easily gets upset when things don't make sense. She has no formal diagnosis but does suffer with a short concentration span, immaturity, and aggression. " *adult*

" He suffers from anxiety and depression and has been on medication for this in the past. " *adult*

First signs

4 years

Among 15 *Unique* members, the first signs of an underlying condition were picked up prenatally in two cases, at birth in four, between four and six months in four, and at two years in one case. Other members were diagnosed with the 22q11.2 microduplication during family testing after a relative was found to have the condition.

Prenatally, one baby had choroid plexus cysts (fluid-filled pockets in the lining of the brain ventricles) on the first pregnancy ultrasound scan. These resolved, but a diagnosis of duodenal atresia (blockage in the bowel) followed, and an enlarged kidney. As a result of these concerns, an amniocentesis was performed. In the second case, pregnancy ultrasound showed a 'thick coating' on the spine and a cleft palate was found at birth.

The babies who raised concerns in the newborn period all had multiple signs, but these signs were highly variable: one baby had breathing difficulties and seizures; another had feeding difficulties, a 'fuzz' of hair over the body and, later, developmental delays; another had a very floppy neck, was small and went on to walk and talk late; another looked 'a little different' and couldn't breastfeed, and became a poorly baby who failed hearing tests and missed developmental milestones.

Among the babies diagnosed in the middle of their first year, one baby had unusual facial features and global developmental delay; another had delay and a refusal to wean onto solid food; two others just missed their developmental milestones. A further child was diagnosed at two years with apraxia, a disorder characterized by inability to carry out skilled movements, despite having the desire and the physical ability to perform them.

" The community doctor wasn't convinced, but I felt there were so many things wrong in so many different areas that something didn't make sense "

Pregnancy, birth and the newborn period

We have some information on 28 pregnancies. Some proceeded normally and where they did not, no specific pattern of abnormality was evident. In one pregnancy there was intermittent bleeding throughout and the baby was born at 36 weeks. One mother noticed little fetal movement. Six mothers had pre-eclampsia (a pregnancy complication) and one also had diabetes of pregnancy and the baby's heart slowed markedly. In one pregnancy, there was little amniotic fluid; in another, a large amount of amniotic fluid.

Babies were born between 25 and 41 weeks.

In the newborn period, four babies needed oxygen. Three babies had very low Apgar scores at one minute. One baby breathed well at first but stopped breathing a few hours later. One baby was diagnosed with a heart murmur; one arm turned blue at three days. Three babies who were not born prematurely had jaundice and three had a low blood sugar (hypoglycaemia). Four babies had noticeably noisy breathing, in one case treated with nebulised medications. In another case, the noisy breathing was put down to being intubated, in two other babies, to tracheomalacia (unusually floppy airways) and resolved naturally in time. Two babies had low muscle tone (hypotonia). One baby had torticollis (wry neck), only ever turning his head to the right, so his head took on an unusual shape. One baby screamed a lot and had difficulty sleeping.

Feeding was difficult in six babies, and one was spoonfed; one had reflux (*see below*); two had a feeding tube. Babies usually stayed in hospital for two to four nights, in one case less than 24 hours. One baby was in special care for two weeks and in hospital for three weeks as she had spells of stopping breathing. One baby stayed in hospital for over two months, requiring surgery to correct a gastrointestinal malrotation and obstruction, placement of a gastrostomy tube and a Nissen fundoplication (*see below*) (Portnoï 2005; Courtens 2008; Wentzel 2008; Lundin 2010; Schramm 2011; *Unique*).

A recent report has investigated studies on thickened nuchal translucency seen on pregnancy scans. Four babies out of 1,696 had a 22q11 duplication. When looking at the group of babies with a chromosome disorder, 22q11 deletions occurred most often followed by 22q11 duplications (Grande 2015).

Feeding

There is some information on feeding issues for 22 babies, children and adults. While some babies and children had no feeding issues and went on to have a healthy and varied diet, feeding difficulties were common among *Unique* members - frequently starting in the newborn period when babies lacked the energy, coordination or ability to suck strongly enough to meet their own nutritional needs. Feeding difficulties can persist for weeks or even months, even in babies with a normal palate, and lead to a diagnosis of failure to thrive (*see* Growth). Babies with a cleft needed adapted teats or feeders until their palate was repaired. After that, they were generally able to eat normal family foods. In some cases early feeding difficulties led on to difficulties handling solids at weaning, and later a generally poor appetite. Two babies, one of them born with major gastrointestinal complications, fed so poorly that they needed a gastrostomy tube placed to allow feeding direct to the stomach.

One week old

Gastro-oesophageal reflux was also common, affecting around half of all babies, and persisting in some cases into childhood. In reflux, feeds and stomach contents return into the gullet and are often vomited or may be inhaled, raising the risk of chest infections, known as aspiration pneumonia. There are many simple measures to control reflux, including positioning semi-upright for feeds and using a cot with a raised head end, and your doctor can prescribe medication to help feeds stay down and counteract any effect of acidity on the food passage. If this is not enough, a surgical operation called a fundoplication can improve the action of the valve that normally prevents reflux from the stomach.

Four children had chronic constipation and one case stool impaction, eventually successfully treated with a laxative after increased fibre and probiotics failed to resolve the problem. Two babies had multiple food allergies.