Inform Network Support

Rare Chromosome Disorder Support Group,
G1, The Stables, Station Rd West, Oxted, Surrey RH8 9EE, United Kingdom
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Facebook group for 7q11.23 duplication families
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7q11.23 duplication syndrome
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A 7q11.23 duplication means that the cells of the body have a tiny amount of additional genetic material from one of their 46 chromosomes – chromosome 7. For healthy development, chromosomes should contain just the right amount of genetic material (DNA) – not too much and not too little. Like most other chromosome disorders, having an extra part of chromosome 7 may increase the risk of birth defects, developmental delay and learning difficulties. However, the problems vary.

Background on Chromosomes

Chromosomes are structures found in the nucleus of the body’s cells. Every chromosome contains thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information telling the body how to develop, grow and function. Chromosomes (and genes) usually come in pairs with one half of each chromosome pair being inherited from each parent. Humans have 23 pairs of chromosomes giving a total of 46 individual chromosomes. Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest in size. Each chromosome has a short or petit (p) arm (shown at the top in the diagram below) and a long (q) arm (the bottom part of the chromosome).

Chromosome Duplications

A sperm cell from the father and an egg cell from the mother each carry just one copy of each chromosome. When they join together they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes can break off or become arranged differently from usual. People with a 7q11.23 duplication have one intact chromosome 7, but the other copy of chromosome 7 has a tiny extra piece of the long arm. Therefore it is believed that most of the clinical difficulties are probably caused by having three copies (instead of the usual two) of a number of genes. We are still learning about the specific jobs or functions of the genes in this region (see Ongoing Research into chromosome 7q11.23 on page 17). Also, it is important to keep in mind that a child’s other genes, environment and unique personality also help to determine future development, needs and achievements.

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

If one person in a family with a duplication of 7q11.23 is mildly affected, will others in the same family also be mildly affected?

Not necessarily. There is a lot of variation between different members of the same family. We know that if one person is mildly affected, others may be more severely and obviously affected.

Could my child with a 7q11.23 microduplication have similarly affected children?

Yes, this is perfectly possible in just the same way as a parent with the duplication can pass it on. We have not known about the condition for long enough to be certain if it affects fertility but as there are many examples of parental transmission it is likely that fertility will be normal. In each pregnancy, someone with the duplication theoretically has a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the duplication. Their ability to look after a child is very likely to be closely related to any learning difficulty they may have themselves (Van der Aa 2009; Velleman 2011; Morris 2015).
Why did this happen?

A blood test to check both parents’ chromosomes is needed to find out why the 7q11.23 duplication occurred. In around 3/4 cases the 7q11.23 duplication occurred when both parents have normal chromosomes. The term that geneticists use for this is de novo (dn) which means ‘new’. De novo 7q11.23 duplications are caused by a mistake that occurred when the parents’ sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined.

Some people - about 5-6% of the general population - have an inversion on chromosome 7, where the piece of the chromosome that is duplicated in a child with the 7q11.23 duplication has broken out, turned round 180 degrees, and reinserted itself into the chromosome. A parent who has this inversion will not have any clinical effects from it, but it is possible that the 7q11.23 duplication (or deletion) in a child is more likely to occur.

Children from all parts of the world and from all types of background have 7q11.23 microduplications. No environmental, dietary or lifestyle factors are known to cause them. So there is nothing that either partner did before or during pregnancy that caused the duplication to occur and equally nothing could have been done to prevent it.

In around a quarter of families, the duplication is passed from parent to child. Sometimes the signs in both parent and child are very subtle. In other families, the signs in either the parent, the child or both are more obvious (Kriek 2006; Berg 2007; Morris 2015).

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 7q11.23 duplication or any other chromosome disorder. Where one parent has an inversion of 7q11.23, the possibility of having another child with the duplication (or deletion) is possibly increased. Where one parent has the same duplication as the child, the possibility of having another child with the duplication can be as high as 50 per cent.

Looking at 7q11.23

Chromosomes can’t be seen with the naked eye but if they are stained and magnified under a light microscope it is possible to see that each one has a distinctive pattern of light and dark bands that look like horizontal stripes under a microscope. In the diagram of chromosome 7 on the right the bands are numbered outwards starting from where the short and long arms meet (the centromere). A low number such as q11 is close to the centromere, while a number such as q35 would be further away. Band 7q11.23 is close to the centromere and the part duplicated contains around 1.4 million base pairs (1.4Mb). This sounds a lot but it is actually tiny and is one per cent of the DNA on chromosome 7. Chromosome 7 has around 158 million base pairs and is about five per cent of the total DNA in our cells. Base pairs are the chemicals in DNA that form the ends of the ‘rungs’ of its ladder-like structure.

The extra piece of material on chromosome 7 is so tiny that you can’t see it even under the highest-powered microscope. So the results of a conventional chromosome analysis are likely to give a normal result. Some children are tested more than once, each time with a ‘normal’ result. The duplication can usually only be found using molecular or DNA technology, in particular a technique known as array-CGH or microarrays, that shows gains and losses of tiny amounts of DNA throughout the chromosomes. This technique can which of the 26 genes that are found in band 7q11.23 have been duplicated. These genes are listed in the diagram on page 17. People who have extra material on a chromosome are said to have a duplication but when the amount of material is so small that it can’t be seen even under a high-powered microscope, it is called a microduplication. 7q11.23 microduplications are often referred to as 7q11.23 duplication syndrome or Dup7q.

7q11.23 and Williams syndrome

People who have lost this segment of chromosome 7 have a well-known syndrome called Williams (or Williams-Beuren) syndrome. Williams syndrome (caused by a deletion) has been diagnosed and reported very much more often than the 7q11.23 duplications occur. It is estimated that 7q11.23 duplications occur in 1:7,500-20,000 people (Van der Aa 2009; Velleman 2011; Morris 2015).
Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point where the chromosome has broken in your child. You will almost certainly be given a karyotype which is shorthand notation for their chromosome make-up. With a 7q11.23 duplication, the results are likely to read something like one of the following examples:

46,XY,dup(7)(q11.23q11.23)

- 46: The total number of chromosomes in your child’s cells
- XY: The two sex chromosomes, XY for males, XX for females
- dup: A duplication or extra genetic material
- [7]: The duplication is from chromosome 7
- [q11.23q11.23]: There are two breakpoints in the chromosome, both in band 7q11.23 indicating a small duplication

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

46,XX,ish dup(7)(q11.23q11.23)(RP11-805G2++)dn

- 46: The total number of chromosomes in your child’s cells
- XX: The two sex chromosomes, XY for males, XX for females
- ish: The analysis was by fluorescence in situ hybridisation (FISH)
- dup: A duplication, or extra genetic material
- [7]: The duplication is from chromosome 7
- [q11.23q11.23]: There are two breakpoints in the chromosome, both in band 7q11.23 indicating a small duplication
- (RP11-805G2++): A DNA fragment of interest known as RP11-805G2 has been found in two copies instead of one + as you would normally expect
- dn: The duplication occurred de novo (or as a ’new event’). The parents’ chromosomes have been checked and no duplication or other chromosome change has been found at 7q11.23. The duplication is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

Ongoing research involving 7q11.23

The features of a 7q11.23 duplication are likely to be a result of the extra copies of a number of different genes found in this region. The duplication is generally around 1.5Mb and encompasses 26 genes (Somerville 2005; Depienne 2007; Merla 2010; Morris 2015).

Since speech delay is a common feature affecting those with a 7q11.23 duplication there are efforts by researchers to identify the gene(s) that may play a role in language development. However, since research into 7q11.23 duplications is in its infancy, it is not yet clear which of the 26 genes in this region is likely to have a role.

The genes GTF21 (general transcription 2-1) and CYLN2 (cytoplasmic linker protein-115) have been suggested as being involved with learning difficulties, but further studies are needed to determine whether they have a role in the difficulties seen in people with a 7q11.23 duplication (Van der Aa 2009).

The GTF21 gene has also been suggested to play a role in the separation disorder that affects some people with a 7q11.23 duplication (Mervis 2012).

It is important to remember that while identifying the gene(s) responsible for certain features of a 7q11.23 duplication is interesting and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is duplicated it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.
Sleep
The majority of children go to bed easily at bedtime and sleep well. However, sleep problems affect some children. One unique child continues to have night-wakings and wakes up very early in the morning. Three unique children who are poor sleepers were prescribed melatonin; even with medication one takes a long time to fall asleep and has problems staying asleep. A further unique child has frequent waking. Sleep problems have also been noted in the medical literature (Somerville 2005; Berg 2007; Unique).

Puberty
There is very little information available on puberty in those with a duplication of 7q11.23 but it seems likely puberty generally proceeds as normal at the usual age (Kirchoff 2007; Unique).

Adults with a 7q11.23 duplication
Nineteen adults only discovered they carried the duplication after the diagnosis of their child or grandchild. One has no medical concerns and works independently; another finished school and has no developmental delays; another had seizures as a child and had impaired language processing and expression skills and trouble with articulation (Kriek 2006; Berg 2007; Torniero 2008).

In one study, information on seven of the parents who transmitted the duplication to their children was collected. One father who passed the duplication on to two children had learning and behavioural difficulties (including anxiety and aggression) and language impairment. One mother had a history of language and motor delay but completed normal school and works as an office clerk. She has joint laxity. Another mother has mild learning difficulties together with autistic features such as poor eye contact. Another mother works as a care assistant but reported that she did not do as well at school as her siblings. Another mother did not speak until the age of 5 years and had congenital clubfeet and as an adult works as a saleswoman. Another mother had a history of learning difficulties and now works as a bus driver. A father has a history of learning difficulties and social impairment and was in special education. He was recently diagnosed with autism and self-harming behaviour (Van der Aa 2009).

Some of the parents had a history of motor and language delay or learning difficulties which eventually resolved and in adult life parents are usually employed and functioning well (Van der Aa 2009).

A 23-year-old man is also reported in the medical literature. He has learning difficulties and poor social skills but lives alone. He has been diagnosed with Asperger’s syndrome (Kirchoff 2007).

An 18-year-old Unique member is at college (Unique).

Eight adults were diagnosed following the diagnosis of a child or grandchild. All had some difficulties with speech although not enough symptoms to have been diagnosed with speech delay. Most had learned to compensate well for their difficulties (Velleman 2011).

Why are people with a 7q11.23 duplication so different from each other?
We don’t understand this properly yet but a person’s genes and environment play a role.

Most common features
More than 120 people have been reported in the medical literature, including five series of clinical cases (Berg 2007; van der Aa 2009; Dixit 2013; Morris 2015; Parrott 2015). Unique has more than 40 members. These large numbers mean that the features that are most striking and most common can be identified:

- Speech and language delay, usually the first delay noticed
- Typically low average learning ability, or mild to moderate learning difficulties
- Generally normal growth (although a few people have growth delay before and after birth)
- Vulnerability to anxiety and attention difficulties
- Constipation
- Low muscle tone and an unusual stance and walking style, adding up to Developmental Co-ordination Disorder
- A large head. There may be structural differences in the brain
- Subtle but recognisable facial features
- Constipation
- Enlarged aorta [blood vessel leading from the heart to the rest of the body].

Are there people with a 7q11.23 duplication who are healthy, have no major birth defects and have developed normally?
Perhaps. In around one in four families with a child with the duplication, either the mother or the father has the same 7q11.23 duplication as the child and appears to be unaffected by it. However, in one large series, a geneticist was able to make the diagnosis even in adults who thought they were unaffected (Kriek 2006; Berg 2007; Van der Aa 2009; Velleman 2011; Morris 2015).

What is the outlook?
We can’t be certain yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan.
**Pregnancy and birth**

Unique’s experience has been that mothers carrying babies with a 7q11.23 duplication generally experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth [Unique]. However, a large survey including 53 birth records found some kind of pregnancy problem in eight. Nine babies were born prematurely between 27 and 36 weeks. Eight babies needed intensive care for respiratory distress. Almost half the newborns appeared healthy, but just over half had something noteworthy, and four had multiple anomalies. Features noted most commonly among newborns include a large head and unusual facial appearance. Birth anomalies were found in many body systems: the head and brain; heart; kidneys; genital system; adrenal glands; airways; oesophagus (food passage); bowels; bones; and limbs [Morris 2015].

**Growth**

Babies are often, but not always, of above average weight at birth. In a series of 53 babies, 28 per cent were at or above the 95th centile. However, a few babies are small and underweight at birth, and birth weights recorded at Unique and in the published medical literature show a considerable variation [Depienne 2007; Torniero 2007; Morris 2015; Unique]. The baby’s head is likely to be large: among 37 newborn babies, the average head circumference was at the 75th centile, with 11 babies at or above the 95th centile, and no babies at or below the 25th centile [Morris 2015]. It is recommended that all babies’ heads are regularly measured.

**Range of birthweights at Unique [at or near term]:**

2.721 kilos (5lbs 16oz) to 4.649 kilos (10lb 4oz)

Most babies and children identified so far have shown a normal growth rate after birth, although some have growth delay and remain short. Overall, no consistent effect on growth has been found, and growth hormone shortage has been found in less than 1 in 10. It is recommended however, that growth is monitored in all children [Somerville 2005; Berg 2007; Depienne 2007; Van der Aa 2009; Morris 2015; Unique].

**Feeding and Constipation**

Most babies and children do not have feeding problems and many are able to successfully breastfeed, although one or two needed tube feeding at first [Somerville 2005]. Three out of 53 babies in a large survey had a longer than normal stay in hospital because of difficulties with latching on, and four needed feeding by tube direct to the stomach [Morris 2015]. Unique data show that many babies (6/7) have gastro-oesophageal reflux (where feeds and stomach contents return into the food passage and are often vomited or may be inhaled, causing chest infections, known as aspiration pneumonia) but this has generally been well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head end of the bed for sleeping. If these measures are not enough, prescribed medications or anti-reflux milk are usually enough to keep feeds down. Reflux has been described much less frequently in the medical literature, in 4/53 babies and children in the largest series. In only one case was reflux serious enough for hospital treatment [Berg 2007; Torniero 2007; Morris 2015; Unique].
Behaviour

Researchers have drawn attention to the overlap between atypical behaviours in very young children with a 7q11.23 duplication and those with an autistic spectrum disorder (ASD) so that children may first be evaluated for autism though they may not formally meet the diagnostic criteria. Two Unique children have a diagnosis of pervasive development disorder – not otherwise specified (PDD-NOS), an ASD which tends to be milder than autism. However, the specific behaviours and their severity vary between individual children. One study suggests that people with a 7q11.23 duplication and ASD often have a highly sociable personality with people they know and are comfortable with (Berg 2007; Van der Aa 2009; Sanders 2011; Velleman 2011; Unique). Repetitive movements, repetitive behaviours, repetitive speech, using another person’s hand as a ‘tool’, limited facial expressions, excessive orderliness (lining up toys), lack of emotional interest, sensory integration problems, difficulty switching routines and avoiding social gaze or contact have been identified in individual children. A diagnosis of autism can be extremely helpful in accessing services and tailoring the educational and behavioural therapy to meet the specific needs of a child with autism. It is possible that some behaviours lessen and may vanish once speech emerges. This suggestion fits with the description of one 13-year-old girl as ‘socially normal – naïve, loving and quiet’ (Torniero 2007). This is also backed up by a study of 30 children which found that although children had behaviour consistent with ASD (including shyness and repetitive behaviours), the children also had important characteristics that are not consistent with ASD. For example, in play sessions with their parents, the participants had social communication strengths including eye contact and clear pleasure in interacting with their parent, shared enjoyment and creative, imaginative play. The researchers suggest that the reluctance of children with 7q11.23 duplications to engage with people they do not know is likely to be secondary to their speech and anxiety problems (see below) rather than to ASD (Velleman 2011).

Social, stranger and separation anxiety can be quite acute and was scored high by Unique families; one 19-year-old girl suffered from panic attacks (Berg 2007; Unique). A recent study of 42 people with a 7q11.23 duplication found that around three quarters of the children had an anxiety disorder with around a quarter with separation anxiety. Another study involving 27 children (aged 4-13 years) found that just under a third (8/27) had separation anxiety (Velleman 2011; Mervis 2012). Some children, possibly particularly boys, also scored high for aggressive behaviours such as hitting or pinching, although Unique children did not score high for self-harming behaviours such as arm biting. Some children have difficulties with mood control – they get overexcited rather than excited and can quickly lose their temper when frustrated - and many children, notably boys, reported in the medical literature (although fewer

Appearance

Babies and children with this duplication would usually not stand out from a crowd of other children. However, specific facial features have been seen in up to half of all children and together these add up to a typical, recognisable facial appearance. These features include a large head; straight and neatly placed eyebrows, a high broad nose, a broad, prominent forehead, and an asymmetric face (Somerville 2005; Berg 2007; Torniero 2007; Van der Aa 2009; Velleman 2011; Morris 2015).

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

Some children with a 7q11.23 duplication will have entirely normal physical development, but others are a little slow to reach their developmental motor milestones. Delays in learning to crawl and walk in comparison to other children are common, but are generally overcome by school age. Almost everyone described in the literature and known to Unique was fully mobile although some older children still had minor problems with balance and gait. Despite this good news, three quarters of children in one series met the criteria for developmental co-ordination disorder, with low muscle tone, and atypical standing and walking styles. All children should have a physiotherapy assessment (Somerville 2005; Berg 2007; Depienne 2007; Torniero 2008; Van der Aa 2009; Morris 2015; Unique). In one large series, the age at which children started to walk was between 9 months and 3 years, 9 months (Morris 2015). From other reports, individual babies start to sit between 6 months and 15 months (average 10 months). Independent walking was mastered between 12 months and 2 years, 2 months (average 18 months). In around half of children, there are balance problems and in some, there were difficulties with coordinating both sides of the body, leading to difficulties standing on one leg, hopping, skipping and pedalling (Somerville 2005; Berg 2007; Depienne 2007; Morris 2015; Unique).
One of the causes of the delay in mobility is low muscle tone (hypotonia), reported in as many as 60-70 per cent of children. This makes a child or baby feel floppy to handle and generally improves as children mature and may disappear with physiotherapy and exercises. In a smaller proportion of children, the joints are unusually flexible (Van der Aa 2009; Morris 2015; Unique).

- He runs with an unusual gait and cannot ride a bike without stabilisers. He had a mobility pushchair and Piedro boots” – 7 years
- She continues to benefit from adaptive PE and is still a bit behind peers in motor activity. She is able to do most of the things she should, she is just not as strong/quick/independent/confident. She has learned skipping this year with much assistance” – 8 years
- I would say that every milestone was delayed at least 6 months” - 10 years
- She learned how to ride a bike at 8 years” – 12 years
- “Can be clumsy while walking or running and cannot ride a bike” – 14 years

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

Some children are delayed in controlling their hand use while others develop on time. In one large series, almost three quarters of 31 children had developmental co-ordination disorder. Children were typically described as ‘clumsy, and slow to develop co-ordinated motor skills’. In Unique’s experience, even slow-developing children have learned to feed, dress and care for themselves by school age and while they may take longer to learn how to cut, draw and write than other children, still achieve these skills within a normal or slightly extended timeframe. One boy of 12 was described as ‘impulsive’ when carrying out fine motor tasks but was more controlled when prompted [Somerville 2005; Berg 2007; Depienne 2007; Morris 2015; Unique].

In terms of self care, data from Unique and the medical literature suggest that children may be late to be toilet trained during the day [average age 4 years] and at night. In a child with a borderline or mild learning disability, it may not be appropriate for parents to expect toileting to occur at the same age as in other unaffected children [Depienne 2007; Unique].

- “He cannot cut with a knife and struggles holding pencils” – 7 years
- “All her fine motor skills were delayed and difficult to overcome, from feeding to dressing herself. She had trouble drinking from a cup or using cutlery. She still struggles with using utensils or scissors” – 12 years
- She had difficulty in the past with cutting, tying laces and holding a pencil – all fine now after occupational therapy input” – 14 years

- Hearing
Generally speaking children have had normal hearing, although 3 out of 53 had hearing loss, two needing a hearing aid. Young children frequently have the fluctuating temporary hearing loss caused by a build-up of fluid behind the eardrum (glue ear). Glue ear usually resolves as children get older and the ear tubes widen and become more vertical resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear and glue ear can reduce a child’s hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum [Berg 2007; Morris 2015; Unique].

Two children within Unique failed regular hearing tests despite normal hearing because they did not understand how to respond to noise. Parents may be well advised to draw this to the attention of whoever is doing the screening. One Unique child has been 40 per cent deaf from birth and is now on his second set of grommets (Unique).  

- Genital anomalies
Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. The most common problem is cryptorchidism (undescended testes). The testicles can be brought down by a straightforward surgical operation if they do not descend of their own accord in time. One boy with a shawl scrotum [the scrotum surrounds the penis, resembling a ‘shawl’] has been described and another is described as having small genitalia. Two boys needed a hernia in the groin [inguinal] repaired. Two girls have anomalies of the womb [Berg 2007; Van der Aa 2009; Morris 2015; Unique].

- Kidneys
No kidney problems have been found in most children [18/22 and 10/11 in the largest series], but the problems found included a missing kidney in two children and an adult, all female, and enlarged kidneys [hydronephrosis] in two boys. One baby had small kidneys. It is recommended that girls with a kidney problem have an investigation of their reproductive system [Morris 2015; Unique].

- Skin
A mottled or marbled skin appearance [cutis marmorata] was seen in almost half of the children aged under 14 [Morris 2015]. Other researchers have reported café au lait spots or patches of dark/ light skin [Berg 2007; Torniero 2007].

- Other
Other health concerns reported - which may or may not be linked with the duplication - include flat feet [Berg 2007; Morris 2015; Unique]; cubitus valgus – an increased angle at the elbow making the lower arms stick out more [Berg 2007]; hip dysplasia, corrected by splinting or surgery [Torniero 2007; Unique]; talipes [club feet] corrected with surgery or support shoes [Torniero 2007; Morris 2015; Unique]; torticollis (the head is tilted to one side) which resolved with physiotherapy in one child and improved after an eye operation in the other [Berg 2007; Unique]; osteopenia (low bone density) [Unique].
structure include white matter changes, enlarged ventricles, and a thin corpus callosum (the band of nerve fibres connecting the two sides of the brain) and cortical dysplasia of the left temporal lobe (Berg 2007; Torniero 2007; Morris 2015; Unique).

Four/53 children had hydrocephalus (a build-up of fluid within the brain), and three were treated with a shunt to drain the fluid (Morris 2015).

Some of the structural brain differences are believed to underlie the social difficulties that some people with a 7q11.23 duplication face (Prontera 2014; Morris 2015).

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### Heart problems

As many as half of people with a 7q11.23 duplication have an **enlarged aorta** (blood vessel leading from the heart to the rest of the body). This is a silent condition, and as far as is known, the enlargement remains stable, at least in childhood. However, more studies are needed, and meanwhile yearly cardiac investigation and if necessary more frequent follow-up is recommended (Parrott 2015; Morris 2015).

Otherwise, heart problems have been reported to affect around 20 per cent of people with a 7q11.23 duplication. The most common problem reported in one in seven children is **patent ductus arteriosus** (PDA, failure of the ductus arteriosus (channel between the aorta and the pulmonary artery that takes blood to the lungs) to close). One child had two **ventricular septal defects (VSDs)** which are holes in the wall between the two pumping chambers of the heart (ventricles). This allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Treatment is determined individually. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from extra blood flow. One child had an **atrial septal defect (ASD)** which is 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 (Kriek 2006; Van der Aa 2009; Morris 2015; Unique).

### Joint laxity

A number of children and adults with a 7q11.23 duplication have lax, or loose, joints. Joint laxity has been described in around 1:9 children in the medical literature, but has only been reported in one Unique child (Berg 2007; Van der Aa 2009; Morris 2015; Unique).

### Eyesight

Previously, we have found that eleven children out of forty have some defect of vision or focusing. The most recent report (Morris 2015) found a much lower rate of vision problems, all a form of squint (strabismus). The difficulties reported earlier are usually correctable by the use of glasses, and include a squint [strabismus, inward or outward] seen in three children and/or astigmatism, when the cornea (the clear cover over the iris and pupil) is abnormally curved which has been reported in three children. The effect on vision is to make objects appear blurred. Sometimes the brain can compensate for astigmatism although it may be too strong for this to happen without the aid of glasses. Four people have long-sight (hypermetropia) and three children at Unique have Duane’s syndrome (an eye movement disorder where the eye cannot move outwards) (Berg 2007; Torniero 2007; Van der Aa 2009; Unique).

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### Speech and communication

Speech and language development tends to be strikingly delayed and almost all of those with a duplication of 7q11.23 seem to be affected. Early speech evaluation and therapy is strongly recommended. Children have early delays in learning to express themselves understandably in organised words and phrases. However, all older children and adults who have been fully described do speak and most of them eventually talk in phrases and sentences. Despite this, it is clear that the range, severity and permanence of the effect on speech and language vary a lot between individuals. While children have only spoken their first understandable words between the ages of 12 months and four years, 9 months, their understanding has been generally much more advanced than their ability to talk. Some children have been taught to sign or use picture exchange systems (PECs) and others have used a repertoire of gestures and become reasonably fluent communicators using these methods. Later stages of language development have also been delayed, with vocabulary increasing but not at the rate you would expect in other children and progress to two-word phrases and sentences only after the age of six years. One report suggests that 15 per cent (4/26) have mild language delays; 35 per cent (9/26) have moderate delays and 50 per cent (13/26) have more severe delays. Another recent study of 42 adults and children (aged 18 months to 61 years) found that receptive language skills (understanding of language) were less affected than expressive language (what they are able to communicate). Most of the toddlers in this study had very limited speech and few identifiable, meaningful words. Among 25 children (aged 4-17 years) more than three quarters had verbal apraxia and dysarthria (see box next page), and more than half had articulation problems. This study also looked at eight adults (28-61 years, all diagnosed with a 7q11.23 duplication after a child or grandchild was diagnosed). Most had learned to compensate for their difficulties; the errors they made were primarily in challenging multisyllabic words (eg aluminium) or tongue twisters. Another recent study of 46 children found speech sound disorder in more than 8 out of 10 (Somerville 2005; Kriek 2006; Berg 2007; Depienne 2007; Torniero 2007; Van der Aa 2009; Velleman 2011; Morris 2015; Unique).

One child had speech delay but improved dramatically between the ages of 4½ years and 5 years, coincident with medication for severe anxiety (see Behaviour page 14) (Berg 2007).

Pronunciation difficulties have been obvious, with children only articulating the first syllable of a word or not progressing beyond two-syllable words. When tested, hearing has been normal but specific difficulties making certain sounds of speech (such as l, r) have been described in both children and adults. All children should have a speech and language assessment, and speech therapy is strongly recommended, with sign language and picture exchange communication (PECs) shown to be beneficial when needed (Velleman 2011; Morris 2015; Unique).

**“She can say three word phrases and also uses signing” – 6 years**

**“He was late to start talking and now uses 2/3 word sentences. He also uses PECs and Makaton [sign language]. He has daily speech therapy at school” – 7 years**

**“She sometimes has difficulty figuring out the mouth movements for a new word or phrase and it helps to have her ‘watch my mouth’ to see it first. Generally though she is pretty easy to understand and does not have a lot of mispronunciations” – 8 years**

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Verbal apraxia – a person has trouble saying what he or she wants to say correctly and consistently. It includes speech planning symptoms such as speech that takes lots of effort; difficulty putting sounds and syllables together in the correct order to form words. Another common characteristic of apraxia of speech is the incorrect use of “prosody” — that is, the varying rhythms, stresses, and inflections of speech that are used to help express meaning.

Oral apraxia – includes non-speech planning symptoms such as groping while trying to protrude the tongue and difficulty producing sequences of oral postures (such as stick out your tongue and smile).

Phonological disorder or articulation disorder – children do not use some or all of the speech sounds expected for their age group.

Dysarthria – non-speech and speech problems such as weakness, low or high muscle tone, or poor co-ordination of the muscles themselves and voice differences.

Learning

The range of learning ability varies widely. A recent study of 63 children gave a typical low average intelligence score of 85 (1/100), with individual learning abilities ranging from high average to severely impaired. It showed an intelligence score ranging from 79 to 118 (average is 100) in children without specific sound disorder, and from 41 to 107 in children with the speech sound disorder. Another small study suggests that 17% (2/12) have normal intelligence, 50% (6/12) have mild learning difficulties and a third (4/12) have moderate learning difficulties. Most children will attend mainstream school but may need some classroom assistance or special needs lessons; other children benefit from a special education school (Van der Aa 2009; Mervis 2015; Morris 2015; Unique).

The expressive language delay does not appear to lead to a similar delay in reading. In the 63-child study, reading - and mathematics - scores were typically average to low average, with a range of high average/ superior ability to severe impairment (Mervis 2015). In Unique’s experience, children have read well by eight years. Families also report that memory is a strength. It is believed that visuo-spatial reasoning (recognizing visual patterns and drawing inferences from them) is relatively protected in most children with a 7q11.23 duplication, although this is not true of all. One study found that children with 7q11.2 duplications performed well at non-verbal reasoning (Berg 2007; Torniero 2007; Van der Aa 2009; Velleman 2011). Unique families report that their children draw relatively well and in an interesting way.

A study looking at literacy skills in 12 school-aged children (7-15 years) found that those taught to read by phonics (9/12) had reading skills in the average for the general population range. The children taught primarily with sight-word methods (3/12) had more difficulty with mild disability to low average range (Velleman 2011).

Most likely features

- Generally good health

Reports show that most people with a 7q11.23 duplication enjoy good health. As children they have the same frequent upper respiratory tract infections as other children but outgrow the tendency by six to nine years of age. Two children had their tonsils and adenoids removed, in one instance motivated by an attempt to solve sleep apnoea. One child had urinary reflux, corrected surgically (Berg 2007; Van der Aa 2009; Unique).

- Palate

Four babies out of a total of 34 were born with a cleft lip or palate or both and a further baby was born with an unusually high palate (Somerville 2005; Berg 2007; Unique). A cleft is caused by an error in fusion when the fetus is forming. The lip and palate fuse from pieces that start on opposite sides of the head. The lip fuses around weeks 6-7 and the palate at around 12 weeks. A cleft occurs when the pieces come round but do not join.