Support and Information

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Duplications of 4q

Facebook page for 4q duplications:
www.facebook.com/groups/544157182329865

Unique lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.
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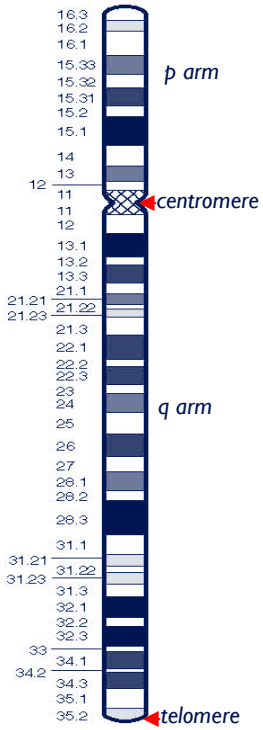
Duplications of 4q

A duplication of 4q means that there is extra material from one of the body's 46 chromosomes – chromosome 4. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Extra material is likely to disturb development but how obvious and serious the effect is depends on the amount of duplicated material, on which part of the chromosome is duplicated and on what genes are disturbed by the position of the breakpoint.

Chromosomes are the structures in the nucleus of the body's cells that carry genetic information in the form of genes that tell the body how to develop, grow and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. So chromosome 4 is one of the largest chromosomes. Each chromosome has a short (**p**) arm (at the top in the diagram on the right) and a long (**q**) arm (at the bottom in the diagram). A duplication of 4q means that the extra material is from the long arm of chromosome 4.
A duplication of 4q can also be called **partial trisomy 4q**.



Chromosome 4

Looking at 4q

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands. You can see these bands in the diagram. They are numbered outwards starting from the point where the short and long arms meet (the **centromere**). A low number such as q11 is close to the centromere. A higher number such as q35 is closer to the tip (the **telomere**).

Many people have been described in the medical literature with loss or gain of material from another chromosome arm as well as the 4q duplication, usually as a result of a chromosome change known as a translocation. As these people do not show the effects of a 'pure' duplication, they are not considered in this leaflet. *Unique* holds a list of these cases in the medical literature and the karyotypes of those in *Unique*, and this is available to members on request.

Sources & references

The information in this leaflet is drawn from what is known about 43 people with a duplication of 4q. Thirty people have been described in the medical literature with a pure duplication of 4q without loss or gain of material from any other chromosome arm. 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. If you wish, you can obtain most articles from *Unique*. The leaflet also draws on *Unique*'s database. When this leaflet was written, *Unique* had 15 members with a pure duplication of 4q. (The total doesn't add up to 43 because some *Unique* members are the subject of reports in the medical literature.)

Can it happen again?

The possibility of having another pregnancy with a 4q duplication depends on the parents' chromosomes. If both parents have normal chromosomes (in 70% of cases (Thapa 2014), the duplication is very unlikely to happen again.

If either parent has a chromosome rearrangement involving 4q (in approximately 25% of cases (Thapa 2014), the possibility is greatly increased of having other affected pregnancies. If they wish, parents should have the opportunity to meet a genetic counsellor to discuss the 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 very accurate, although not all of these tests are available in all parts of the world.

Could my child with a 4q duplication have similarly affected children?

There are quite a few families in which a small duplication has been passed directly from one parent to one or more of the children. One is a duplication of 4q31.1q32.3, passed on by a mother to two of her four children (Goodman 1997). Another is a family with a duplication of 4q31.3q33, in which the mother passed it on to two of her children (Maltby 1999). In another family with two affected children, it is likely that the inverted 4q35.2q31.22 duplication came from one of their parents; however, as both parents were not tested, this cannot be certain (Otsuka 2005). Someone with the 4q duplication has a 50 per cent risk of passing it on. A geneticist would be able to give you more information.

"Where on earth do we start? He is the most generous, caring, empathetic child who has made me the parent I am today. He taught me to stop and appreciate the everyday things that otherwise fly right by us with nary a glance. He is a beautiful, beautiful child who makes my heart feel like it's going to burst."

Other illnesses

Individuals with a 4q duplication have developed other illnesses. Where only one person is affected, it is not possible to make any clear link between the chromosome anomaly and the illness. A baby with a 4q25q31 duplication developed pyloric stenosis (blocked passage between stomach and small intestine) as a newborn and needed surgery; children with a 4q28q35 duplication and with a 4q21q35 duplication were found to have a low thyroid level (Bueno Martinez 1991; Gorukmez 2014; *Unique*). A 31 year old woman with a 4q21.2q28 duplication developed Parkinsonism. Parkinsonism is a movement abnormality leading to uncontrollable tremor in the hands and arms and deterioration of gait. She also had a delay in motor development and a severe cognitive deficiency (she could not read or write). The cause is probably the extra copy of the SCN5A gene. The symptoms improve with medicines (Garraux 2012).

Eyesight

Most children with a 4q duplication have normal eyesight. A minority of children are shortsighted or have a squint (strabismus) looking inwards, outwards, up or down (Bueno-Martinez 1991; Halal 1991; *Unique*). The main effects of strabismus are that usually the person will have one eye which is stronger than the other. Treatment depends on the cause but can include patching the stronger eye, exercises, glasses to correct a refractive error such as long sight and surgery to realign the muscles that hold the eye in place.

Hearing

Most children with a 4q duplication have normal hearing. Individuals have had a hearing impairment in one ear or both, but this is not necessarily connected with the 4q duplication (Lundin 2002; Maltby 1999; *Unique*).

Teeth

Generally speaking, children with chromosome disorders appear to have more dental problems than others. Information on ten children in the group shows that in four children the teeth were unusually long or short and one child with a cleft lip had front teeth of different sizes; in one child the teeth emerged very late; one child had a divided lower front tooth; two children have under- or overbite, caused by a mismatch between the teeth of the upper or lower jaw; two children have a very small jaw and will need teeth removed due to overcrowding; one child faces difficulties with dental work because of having a very small mouth. In one child the teeth decayed fast and needed extensive work (Lundin 2002; Muraki 1997; Jeziorowska 1993; Taylor 1977; Vogel 1975; *Unique*).

> “ His teeth are shocking although the dental clinic at the hospital thinks that considering his special needs, the condition and state of his teeth is pretty good. But they are very crooked and crowded. The last dental check (done under a general anaesthetic) saw five teeth removed due to holes and/or being loose.
> Any dental work is also done under a general anaesthetic as there is NO chance of getting him to even sit in a dentist’s chair, let alone let them do something to him in there. ” - *4q28q35 duplication*

The karyotype

Your geneticist or genetic counsellor will be able to tell you about the breakpoints in your child’s chromosome 4. Your child will probably be given a karyotype, a shorthand notation for their chromosome make-up. It is likely to read something like this **46,XX,dup(4)(q27>q35.1)de novo** or **46,XX,dup(4)(q35q35)(DJ963k6++)**

46 The total number of chromosomes in your child’s cells
XX The two sex chromosomes:XX for females; XY for males
dup A duplication, or material has been repeated
(4) The duplication consists of material from chromosome 4
(q27>q35.1) The chromosome has broken in two places. The first break is at q27 and the second break is at q35.1 so these are the ends of the duplicated section.
de novo The parents’ chromosomes have been checked and no duplication or other abnormality found. The duplication has not been inherited.
(q35q35) There is an extra copy of band q35
(DJ963k6++) The extra (duplicated) material contains the genetic marker DJ963k6. There is normally one copy of this marker. The ++ sign shows that there are two copies of the marker.

Is there a 4q duplication syndrome?

It’s true that certain features - such as unusual thumbs and kidneys - are found more often in babies and children with a 4q duplication. However, many other babies and children have perfectly normal kidneys and thumbs. Individuals with a 4q duplication can be as different from each other as they are similar. Even identical twins, each with the same 4q duplication, were affected very differently (Celle 2000). Overall we can’t identify a clear enough pattern of similarities to say that there is a 4q duplication syndrome.

New syndromes may in the future be identified for short segments of 4q. But pure 4q duplications are very rare and even if new syndromes are found, there will still be marked differences between individuals.

Are there people with a 4q duplication who are healthy, have no major medical problems or birth defects and have developed normally?

Yes: in a few people, a small duplication appears to have little effect. This seems to be true most often when the duplication covers just parts of bands 4q31 and 4q32.
A mother with a small duplication from 4q31.1 to 4q32.3 had only difficulty perceiving and identifying objects and characters by touch and distinguishing left from right, while her son who inherited the duplication had a mild degree of delay, as well as hypospadias (the hole at the end of the penis is on the underside) and a small hole in the heart that resolved naturally (Goodman 1997). Another person with a duplication of 4q31.22 to 4q33 had mild difficulties with learning and a somewhat unusual facial appearance (Van Dyke 1988). Three members of the same family have a duplication of 4q31.3 to 4q33: the mother has no clinical problems and the children do not have problems known to be associated with the duplication (Maltby 1999).

A boy with a larger duplication from 4q21.2 to 4q25 also developed normally to the age of three years, although there were concerns over his impulsive behaviour and short attention span (Hegmann 1996). Another boy with a large duplication from 4q25 to 4q34 was healthy and only mildly intellectually delayed (Elghezal 2004).

What is the outlook?

The outlook for any baby or child depends on what part of the long arm of chromosome 4 has been duplicated and how this has disrupted early development in the womb. The most important effect is on the major internal organs, especially the heart. Historically, babies with heart defects have not thrived as well as those born with a healthy heart but improvements in children's heart surgery and cardiac care mean that you cannot always judge the present by looking at the past.

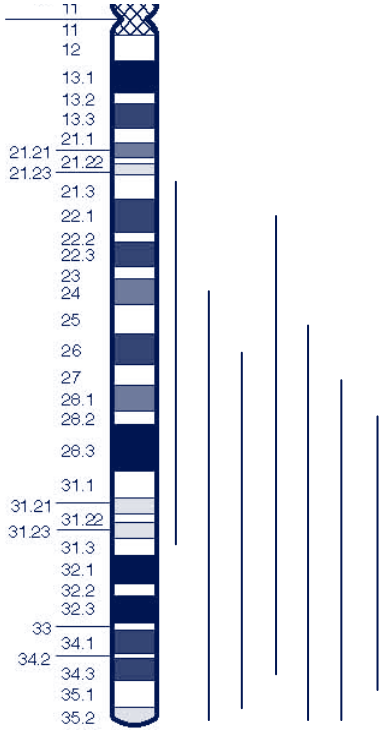
There are many healthy older teenagers and adults with particular duplications and you may wish to compare your child with others with the same duplication. It's important to remember though that the same duplication can have quite different effects on different people. This has been shown very clearly in identical twins, each with a duplication from 4q28.3 to the tip of the long arm, one of whom had a diaphragmatic hernia (a defect in the muscular wall that separates the contents of the abdomen from the chest) which she didn't survive, while her twin was born generally healthy and developed quite well (Celle 2000; *Unique*).

So there will be differences between your child and others with an apparently similar karyotype and these can be quite marked. It is very important to see your child as an individual and not to rely on direct comparisons with others with the same karyotype. After all, each of us is unique.

Growing up, with a duplication from 4q31 to the tip of 4q: 6 months (left); 10 years (centre); 17 years (right).

Growing up, with a duplication from 4q28 to 4q35: 8 days old (left); 10 years (right).

Umbilical hernia



Extent of duplications for babies born with an umbilical hernia

Seven babies were born with an umbilical hernia (Rinaldi 2003; Mikelsaar 1996; Jeziorowska 1993; Taylor 1977; Dutrillaux 1975; *Unique*). An umbilical hernia shows as an abnormal bulge that can be seen or felt at the umbilicus (belly button). The hernia develops when a small opening in the abdominal muscles that allows the umbilical cord to pass through does not close after birth. Part of the lining of the abdomen, part of the intestine and sometimes fluid from the abdomen passes through the opening causing the hernia. Many umbilical hernias close naturally by the age of three or four but a very large hernia or one that stays open after this age can be closed surgically.

Minor genital anomalies

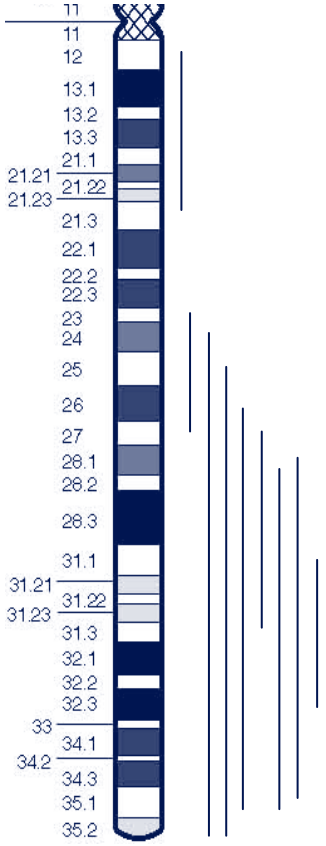
Of 12 boys with recorded information on genital formation, seven had a minor developmental anomaly. Undescended testicles at birth - one or both - are the most common anomaly and one boy was born with hypospadias, where the hole at the end of the penis is on the underside instead. One boy has small testes and a small penis (Elghezal 2004; Rinaldi 2003; Goodman 1997; Muraki 1997; Jeziorowska 1993; *Unique*).

Hypospadias is usually repaired surgically using tissue from the foreskin. Treatment for undescended testicles depends on the suspected cause and is usually needed if the testicles do not descend naturally in time. Generally speaking, the testicles can be brought down in a short operation under general anaesthetic called an orchidopexy.

Infections

Babies and young children with a chromosome disorder appear generally to have a higher rate of childhood infections including ear and chest infections than children with no disorder and this is true of those with a 4q duplication. Episodes of pneumonia may be triggered in young babies by milk or reflux inhalation and chest infections including pneumonia can be a constant winter feature in early childhood (*Unique*).

" As a smaller child he would get spasmodic croup – sometimes bypassing the croup cough and going straight into respiratory distress. These incidents dropped significantly when we changed his diet. "



Extent of duplications for babies born with a heart problem

receive more blood than they should and the heart has to work too hard) and a defect between the upper heart chambers; a baby with an inverted duplication of 4q26q35 also had an open ductus arteriosus, as did a baby with a 4q27 to 4q31.3 duplication; a baby with a large duplication from 4q25 to the tip of the long arm had a truncus arteriosus (a single blood vessel leaving the heart that then branches into vessels that go to the lungs and the body. This great vessel usually sits over both the ventricles and the upper part of the wall between the two chambers is missing, resulting in a VSD); a baby with a duplication of 4q28q35 had defects between both upper and lower heart chambers and an open ductus arteriosus, repaired surgically; a child with a 4q31.1q32.3 duplication had a small VSD that closed naturally by the age of seven. Of these, the baby with truncus arteriosus is known to have died before birth (Hubert 2006; Rinaldi 2003; Celle 2000; Goodman 1997; Halal 1991; Taylor 1977; *Unique*).

Seizures and seizure-like episodes

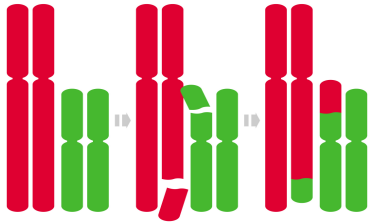
No seizures or seizure-like episodes have been reported in 31 babies and children. Seizures or recurrent 'absences' or 'blackouts' have been reported in eleven people, including six out of 14 *Unique* members. A further child had an abnormal EEG (measurement of patterns of electrical activity in the brain) but no seizures (Hubert 2006; Celle 2000; Muraki 1997; Jeziorowska 1993; Fryns 1980; Dutrillaux 1975; Vogel 1975; *Unique*). The seizures occur regardless of the size or position of the duplication and no 'critical region' makes them more likely. In every case where information is given, seizures were either well-controlled with anti-epileptic medication or resolved naturally, in two cases in babyhood.

Seizures are sometimes associated with abnormal structures within the brain. In babies and children with a 4q duplication, the only abnormalities found were prominent spaces for cerebrospinal fluid but these were not found in children with seizures. A large number of babies and children had an unusually small head (microcephaly) and in five cases the child also had seizures, but more children with microcephaly had not had seizures (Halal 1991; Mattei 1979; *Unique*). A child with a 4q21q35 dupliciation has been described with atrophy of the white matter (Gorukmez, 2014). One child with a 4q26q35.2 duplication had also white matter abnormalities after an MRI of the brain (Topcu 2014).

How did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 4q duplication occurred. Most 4q duplications are accompanied by a loss of material from another chromosome and are the result of a rearrangement in one parent's chromosomes (Celle 2000; Shashi 1999).

This is usually a rearrangement known as a **balanced translocation** in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. Balanced translocations involving one or more chromosomes are not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers.



A balanced translocation

Some 4q duplications occur when both parents have normal chromosomes. The term that geneticists use for this is **de novo** (**dn**). De novo 4q duplications are caused by a change that occurred when the parents' sperm or egg cells were formed.

Very occasionally, a parent with a small duplication can pass it on to their children. In each pregnancy, a parent with the duplication is likely to have a 50 per cent probability of passing it on and a 50 per cent chance of having a child without the duplication (Maltby 1999; Goodman 1997).

What is certain is that as a parent there is nothing you did to cause the 4q duplication and nothing you could have done would have prevented it. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. It is no-one's fault.

Mother and daughter with the same duplication between 4q31 and 4q33

Generally speaking: Proximal duplications

When the duplication consists of material from near the centromere, it is called 'proximal'. Very few cases have been described in the medical literature or within *Unique*, but from the limited evidence it seems that babies and children with very small duplications of 4q11 to 4q13 are usually healthy and of normal height and the main effect is developmental delay with a degree of learning difficulty or disability. When the duplication is larger and includes bands 4q21 or 4q22, health problems involving the heart or kidneys are more likely (Shashi 1999; Zollino 1995; Estop 1993; Mattei 1979; *Unique*).

Generally speaking: Distal duplications

When the duplication consists of material from closer to the tip of the chromosome, it is called 'distal'. Generally speaking, babies and children with duplications involving bands 4q21 to 4q35 may share some features, including thumb and kidney anomalies as well as developmental delay and certain facial features (a high bridge to the nose, small skinfolds across the inner corners of the eyes, unusual ears and a short groove between the nose and the upper lip (Shashi 1999).

Your baby at birth

Babies' condition at birth is variable. Some babies are born with a reasonable Apgar score (a measure of general wellbeing on a scale of 0-10), while others need resuscitation. Generally speaking, new babies feed reluctantly or with difficulty and some may have problems coordinating breathing as they feed. Some babies are sleepy and not as active as you might expect. If this is not your first baby you may notice that their facial features are different from their brothers' and sisters'. It is possible that your baby will need to spend some time in special care. This is an anxious time for parents, especially as medical staff may now seek an underlying cause for your baby's problems and take a blood sample to examine the chromosomes.

Birth weights of babies with a proximal duplication were within the normal range and 0/4 babies had a low birth weight (below 2.6 kilos) at term.

Range of birthweights at or near term (proximal):
2.7 kilos (5lb 15oz) to 3.2 kilos (7lb 1oz)

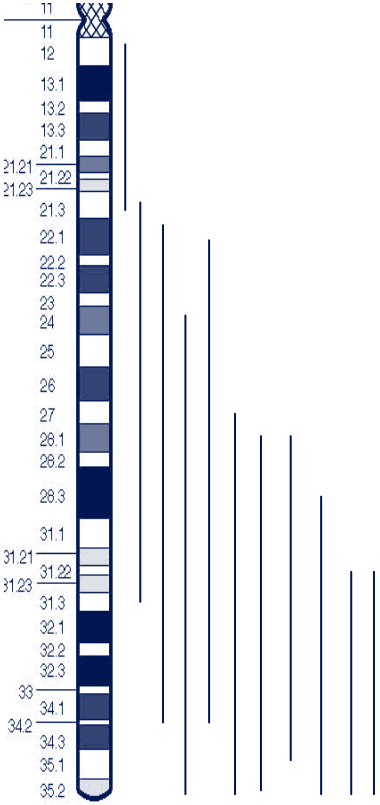
Birth weights of babies with a distal duplication were more consistently low, suggesting that growth delay may start in the womb. Eight out of 22 babies had a low birth weight (below 2.6 kilos) at term and most babies clustered within the lowest 10 per cent of the baby population for weight at birth.

Range of birthweights at or near term (distal):
1.85 kilos (4lb 1oz) to 3.58 kilos (7lb 14oz)

One month old, after premature birth at 35 weeks

Health matters

Kidneys



Extent of duplications for those with kidney problems

Eleven people with a 4q duplication have been described as having an anomaly of the structure or function of the bladder or kidneys; in 32 cases no anomaly has been described or reported.
The types of anomaly are varied, ranging from frequent urinary tract infections or reflux of urine from the bladder up the tubes towards the kidneys (VUR, vesico-ureteric reflux) to small kidneys with normal function (one or both); frequent formation of kidney stones; horseshoe and pancake kidneys (failure of the embryonic kidneys to separate completely; this may or may not affect function); and oligonephronia (reduced number of nephrons, excretion units, in the kidneys with possible implications for high blood pressure and kidney disease) (Otsuka 2005; Lin 2004; Rinaldi 2003; Jeziorowska 1993; Dutrillaux 1975; Vogel 1975; *Unique*).

There is uncertainty whether a 'critical region' exists that must be duplicated for these anomalies to develop. In 10/11 cases including those from *Unique* the child has a duplication that covers 4q31.3 which might represent a 'critical region' for kidney anomalies. However, more people with a 4q31.3 duplication have normal kidney function than do not. Looking at those with both kidney and thumb anomalies, a 'critical region' within bands 4q33q34 has been suggested (Otsuka 2005).

Heart

Most babies with a 4q duplication were born with a healthy heart: nine had a heart defect. It's hard to be certain quite how the 4q duplication affects heart development since no parts of the chromosome arm were particularly associated with heart defects and some duplications had inconsistent effects, with heart defects in some but not in others. While Rinaldi et al (2003) have suggested that 4q26q27 may be a 'critical region' for heart defects, the data do not hold true when *Unique* cases are included. Studies in mice suggest the HAND2 gene may be responsible for the heart defects in persons with a 4q duplication (Tamura 2013).

A child with a duplication at 4q12q21 had multiple holes between the lower chambers of the heart (VSDs); a baby with a 4q23q27 duplication had a complex defect known as tetralogy of Fallot and a hole between the upper heart chambers (ASD), all surgically repaired; a baby with a duplication of the end of the arm from band 4q24 had an open ductus arteriosus (a channel between the aorta and the pulmonary artery that takes blood to the lungs that usually closes shortly after birth. When it stays open, the lungs

Behaviour

Unique has fairly detailed information on the behaviour of seven youngsters with a 4q duplication. There are also brief descriptions of eleven youngsters in the medical literature (Hubert 2006; Maltby 1999; Goodman 1997; Lin 2004; Hegmann 1996; Navarro 1996; Zollino 1995; Fryns 1980). This is too small a number for a definitive picture to emerge but the remarks that follow may give families helpful insights into their own child's behaviour.

Generally speaking, social interactions between children and adults or other children are good and once past an initial shyness, children have shown they can be extremely outgoing and caring people. Many have a good sense of humour and enjoy social and family activities like eating out, dancing, parties, shopping and watching TV together.

> "A lovely child. Very empathetic with others, highly social, communicative and interactive."

> "He is a very easy-going happy kid who his school community accept and adore. He is in a mainstream class at school and I think that has gone a long way to helping him know what is socially acceptable, but we still have many moments where he doesn't realise he needs to stop what he's doing/move away or just give someone a break from the relentless questioning. He needs a lot of help, prompting and guidance – unless we're going to Nana and Granpa's, in which case he is dressed and ready before anyone else." - *4q28q35 duplication*

Among those with a small duplication between 4q31 and 4q33, and others where cognitive function is only slightly affected if at all, there is a tension between expected 'normal' behaviour and what the child may be capable of. Families and medics report some hyperactivity and impulsivity in some children in this group as well as attention deficit and adjustment disorder and difficulties in parent/ child interaction in a family where both parent and children were affected (Maltby 1999; Hegmann 1996; Navarro 1996; Zollino 1995).

> "I work twice as hard to do normal things that I have problems with, but get by in life where it's needed." - *adult*

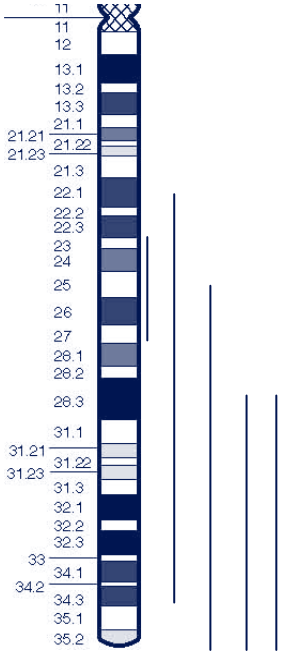
A report in the medical literature describes a brother and sister with a 4q13.1q13.3 duplication and ADHD (Matoso 2013). They have developmental delay and speech problems. Their learning improved after treatment with medicines. The ADHD may be related to the extra copy of the EPHA5 gene.

Among the older teenagers with good cognitive function, mild mood disorders may emerge as a response to social and peer differences and isolation. Appropriate choice of secondary school, inclusive social activities and a low threshold for access to social skills interventions all help.

Among those with larger duplications and those whose cognitive function is more affected, features of challenging behaviour or behaviour that other people find irritating or frightening (screaming; forceful tapping; pulling hair) are likely to be more obvious and youngsters benefit from constant calm reminders of how they are expected to behave. Children are still largely described as sociable but may find it easier to relate to those older or younger than themselves than to children of their own age. *Unique* families report that their children enjoy physical activity (slides, swings, football, going out in wheelchair) and among younger children imaginative play and dressing up are popular.

Sleep problems were unusual, observed in only two out of seven children (Lundin 2002; *Unique*).

Spine



Extent of duplications for babies born with a spinal defect

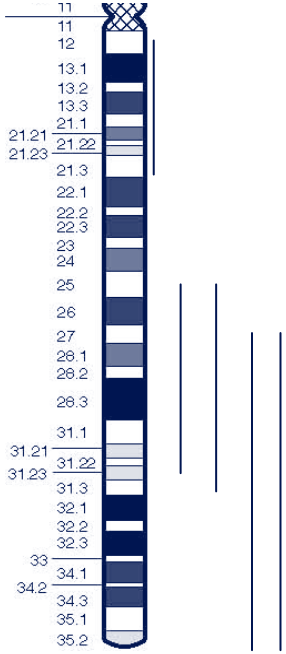
Five/43 babies have been born with a minor defect overlying the spine.

In four cases, there was a deep dimple near the base of the spine, sometimes called a sacral or pilonidal dimple (Celle 2000; Halal 1991; Dutrillaux 1975; *Unique*).

If the dimple is shallow and the end can be seen and it is in the crease between the buttocks, it is not usually a sign of an 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.

One baby was born with spina bifida occulta (Mikelsaar 1996). This is an abnormal development of the bones of the spine and may involve nerves when associated with visible skin changes or a hairy patch.

Cleft lip and/or palate



Extent of duplications for babies born with a cleft lip and/or palate

Most babies are born with an intact roof of the mouth (palate) and a normally formed upper lip. However, five/43 babies were born with a split (cleft) in the palate or a divided upper lip (Lundin 2002; Muraki 1997; Bueno Martinez 1991; *Unique*). Four of these babies share a duplication between 4q27 and 4q31, suggesting that there may be one or more genes necessary for normal palate formation in these bands.

A cleft is caused by an error in fusion when the fetus is developing. 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. Defects in the palate are common in children with and without a chromosome disorder. The hard palate at the front of the mouth may be split or the split may be further back in the soft, fleshy tissue at the back of the top of the mouth. A cleft palate causes difficulties both in feeding and in speech production. Surgical repair eases these difficulties and may eliminate them.

Other problems at birth

Three weeks old; one week after successful surgery to unblock the nasal passages

Individual babies with a 4q duplication have been born with specific anomalies. Where only one person is affected, it is not possible to make any clear link between the chromosome disorder and the anomaly. One child with a 4q28q35 duplication was born with a missing rib; a baby with a 4q28.1q35.1 duplication was born with blocked nasal passages, successfully operated on surgically (choanal atresia); one identical twin had a diaphragmatic hernia; the other had a prominent uterus (Lin 2004; Celle 2000; *Unique*).

A baby with a 4q21q35 duplication had a chronic infection of the gall bladder (Gorukmez 2014). Another baby with a 4q27q35 duplication had Hirschsprung disease (Arayici 2014). Hirschsprung disease is a disorder when part of the colon lacks ganglion cells. This part of the colon cannot pass stools through the colon. This causes an obstruction and swelling of the colon. One baby with a4q25qter duplication had jaundice shortly after birth (Egritas 2010).

Facial appearance

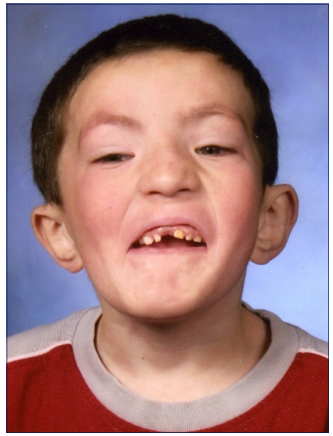
A large number of unusual facial features have been noted by geneticists in reports on babies and children with a 4q duplication. Your baby or child may have just one or two of these features or sometimes more and you may find that he or she looks more like others with a 4q duplication than like other members of your own family. The key features include: an unusually small head (microcephaly, described in 5 persons); sometimes the back of the head is flat (brachycephaly, reported in 11 persons (Thapa 2014) ; thick eyebrows that meet in the middle; hair growth on the forehead; slanting eyes (up or down); eyes set wide apart or unusually close; skinfolds across the inner corners of the eye; a high bridge to the nose; a protruding upper lip with an unusually short (occasionally long) groove between the nose and upper lip; occasionally, a very small mouth; slack muscles around the mouth; ears set lower than normal, sometimes oddly formed; facial asymmetry; small (sometimes receding) lower jaw; a short neck. Most of these features do not affect a child's functioning. Ptosis (hooded, drooping upper eyelids), which also occurs occasionally, can interfere with eyesight and may need surgical correction.

" His smile is turned down a bit but most people can't see anything until they hear him speak and they recognise that he is unique " - *4q27qter duplication*

" An unusual face; because of her features and colouring, some people think she looks like an American Eskimo or someone Asian. " - *4q28q35 duplication*

" There are definite likenesses across our sons but he does look different – he has a flatter nose and a broader bridge across his nose " - *brothers, left with 4q28q35 duplication*

Speech and communication



6 years old, with a 4q27qter duplication

Information on speech and communication is available for only 22 youngsters and in many cases the information is sketchy. This shows that most (19) children have acquired understandable speech and some speak normally (Hegmann 1996). Generally, the development of speech and language appears to reflect the child's cognitive abilities. First words emerged between the ages of 12 months and five years. A child with a 4q13.1q22.2 duplication spoke words from 3 years (Zollino 1995).

However, specific speech and language delay was the presenting concern for at least one child and another showed disproportionate delay in speech and language (Otsuka 2005). One child has profound developmental verbal dyspraxia (*Unique*).

Three children have not acquired speech, but communicate well using gestures and signing. Among those without speech, communication devices are popular and some use is made of sign language as well as gestures and facial expressions. The duplications of those who are not speaking are: 4q11.3q13 mosaic (the duplication is in some of the cells, but not all), as an adult; 4q27qter, at seven years, and 4q27q35.1, as an adult.

Some children have difficulty making particular sounds of speech, including one child diagnosed at six years with a disorder of speech articulation and hypernasal speech (Goodman 1997).

A small minority of babies was born with a cleft in part of the roof of the mouth; even after repair this can affect the quality of speech sounds and so compounds the difficulties that children face. Other children may have a high or short palate that results in velopharyngeal insufficiency and a nasal quality to speech or possibly causes a snorting sound when trying to make explosive sounds such as *p, b, g, t* and *d*.

" He understands quite a bit but unusual or new commands need to be kept to a 2-step process. He expresses very little in terms of adjectives or adverbs and his stories are usually about nouns, actions and positions. Most sounds are difficult to understand because his tongue is 'weak' but he is learning to use an augmentive communication box to help him talk clearly " - *4q27qter duplication at 7 years*

" She has made excellent progress with speech, and now uses 2-3 word phrases and sometimes full sentences. She is easier and easier to understand – but she cannot say *d, l or k* " - *4q28q35 duplication at 11years*

" She needs short, clear instructions " - *4q25q31 duplication at 11 years*

" She does not talk but can make noises and says a few words. Her signing is quite good and she uses a speech machine. At an early age she had more speech, but now uses a few single words. Most sounds of speech present her with difficulties and she cannot blow " - *breakpoint uncertain, 19 years*

Development: hand use, coordination (fine motor skills) and self care

Most children experience delay in hand use. They may have a weak grip, drop things or knock them over easily and find handling small objects a challenge. In *Unique*'s experience, slower-developing children may need help to feed, dress and care for themselves throughout childhood and as adults and master activities such as cutting, drawing and writing only with hand-over-hand support. Some children, probably a minority, achieve relative independence in these activities and this is particularly true of those with a duplication between 4q31 and 4q33 and possibly those with a duplication at 4q12 to 4q13.

As for self care, some youngsters achieve a level of collaborative independence in dressing, washing and personal care tasks. Data from *Unique* suggest that daytime bladder and bowel control may be achieved with a slight to moderate delay, while in some control may not prove consistently possible (Lundin 2002; *Unique*).

" Not very dexterous. His hand writing is appalling! " - *4q28q35 duplication at 10 years*

" She has to be supervised most of the day as she has no road sense and cannot make a drink or prepare something to eat " - *4q25q31 duplication at 11 years*

" Her fine motor skills are fair; she can cut with scissors, colour with a crayon and eat with silverware and can do most things with supervision and repeated reminders. She gets dressed and undressed and makes her lunch with minimal help " - *4q28q35 duplication at 11 years*

" She drops a lot of things and has days when her hands won't do what she wants " - *4q31.3q33 duplication at 17 years*

Learning

Most children will need extra support with learning. How much support usually only becomes apparent over time, and not enough experience has yet built up in youngsters with a 4q duplication to make reliable predictions. However, it seems likely that some children with small duplications in bands 4q31q33 may learn at a fairly normal pace. There is evidence that youngsters with the following duplications have had at most mild learning difficulties: 4q25q34; 4q31.1q32.3; 4q31.22q35; 4q31.3q33 (Otsuka 2005; Elghezal 2004; Maltby 1999; Goodman 1997; *Unique*). Others, with duplications from 4q13.1q22.2, have had a moderate learning disability (Zollino 1995). However, even youngsters with a moderate learning disability are capable of considerable depth and complexity in their learning and may acquire some reading and writing skills.

Other youngsters will need more extensive support and skilled one: one teaching to develop and maintain the skills they need for daily living.

It is important for families to ensure that their child is regularly and thoroughly assessed and placed in a calm, stimulating and supportive learning environment where his or her strengths and abilities are recognised and built upon and any weaknesses minimised.

" She's very good on the computer, can follow simple instructions, open files and write sentences copied down for her. She has a very good memory, can spot any type of car; if you name a make, she can identify it. She learns well because she is very easy-going, keen to learn and please others " - *4q28.3qter duplication at 19 years*

" She has a moderate learning disability and left school with four GCSEs (school-leaving examination taken at age 16). Very quick and bright on computers " - *4q31.3q33 duplication at 17 years*

Hands

Your child's hands may look unusual. They may be small and stubby or long and thin and you may notice features such as incurving fifth fingers, a single palm crease or fingers that thin towards the tip. One thumb or both may be unusual – more like a finger than a thumb, bent, or it may grow from lower down on the hand than normal and the area at the base of the thumb (thenar eminence) may be underdeveloped. Occasionally, one thumb is very small or even missing; also occasionally, there may be an extra finger or the tip of the thumb or finger may be divided (Otsuka 2005; Rinaldi 2003; Navarro 1996; Jeziorowska 1993; Dutrillaux 1975; Vogel 1975; *Unique*).

No parts of the chromosome have been definitely identified with these features, but it has been suggested that when the 4q28.2q28.3 bands are duplicated, the hand structures on the thumb (preaxial) side may not be fully developed while duplication of 4q31.22q32 underlies extra fingers or toes on the thumb side (Lurie 2005). The extra fingers or toes are probably caused by the *HAND2*--gene (Tamura 2013).

In *Unique*'s experience, children cope well but extra digits can be removed surgically.

Feet

Some babies with a 4q duplication are born with feet of an unusual size or position. Feet may be long and thin or short and stubby (like the hands), they may not be the same size, and there may occasionally be features such as a prominent heel, a flat arch, webbing or an unusually large gap between certain toes. Walking is not usually affected, although a child with very flat feet may need special footwear or arch supports. A small minority of babies (4/43) have been born with their feet held at an unusual angle (clubfoot, talipes).

When this occurs, treatment is individually tailored and aims to straighten the foot to grow and develop normally. First-line treatment may include manipulation, casting, taping, physiotherapy and splinting, followed by bracing to prevent relapse. Ankle or foot supports are often prescribed, as well as special footwear. Surgery and sometimes splinting are considered if non-surgical treatments are not completely successful. The foot position may relapse as the child grows and develops, making further surgery necessary.

Feeding

Many newborn babies will have difficulties feeding. Beyond the newborn period, *Unique* has information on feeding histories from 10 children. These show a range of challenges, from difficulties with sucking as a newborn to failure to thrive, managed by long-term feeding by gastrostomy tube direct to the stomach. Many babies have a low muscle tone (hypotonia), which makes feeding and sucking difficult. Breastfeeding may be possible but some babies find the effort too much and thrive better on bottles with teats suitable for premature babies; others are fed expressed breast milk by nasogastric tube. Progress to sipping, chewing and solid foods also tends to be delayed.

" It took a few weeks for his suck to strengthen, but he was then breastfed for the next 18 months. He has always had a love affair with food! That said, anything that requires a lot of chewing is still an issue – I still cut up meat for him into very small pieces and he's not the biggest fan of bread rolls as they require a lot more jaw/chewing than sliced bread " - *4q28q35 duplication, aged 10 years*

Unique data show that some babies and children 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 usually keep feeds down. Constipation is also seen but usually responds to increased fluid, fibre or prescribed medication.

Growth

Front: 17 years old, with a 4q27q35 duplication

Most children and adults with a distal 4q duplication are unusually short and small. Where the duplication includes no more than the last few bands of the long arm or is a small duplication within the 4q31 to 4q33 bands, growth delay is less typical and both children and adults may achieve average heights. Where the duplication is proximal, there is less consistency, with some children achieving expected height for their family, while others show growth delay.

Growth in babyhood and childhood may show a drop-off (Elghezal 2004; Fryns 1980). Adolescent height suggests that those who start small tend to remain short (Lundin 2002; *Unique*).

“ At the age of 17, he is 4’ 6” tall (1.37m) and very light, about 4.5 stone (28.5 kilos). He seems to be growing a little ” - *4q27q35.1 duplication*

“ At the age of 11, she is the same height as her seven-year-old sister ” - *4q28q35 duplication*

“ He was very small until we put him on a low allergy diet and a range of homeopathic supplements – he grew something like 10 cm in three months. At 10, he is now probably average for his age range. He has a long narrow face, a round body and skinny legs ” - *4q28q35 duplication*

Puberty

The little information that exists on puberty suggests that it develops normally at the appropriate age. In one girl with a 4q13q22 duplication, periods started at 9 years and remained regular; another girl with a 4q27q31.3 duplication had premature appearance of secondary sexual characteristics (such as body hair) at the age of seven, with periods starting at 10 years. In *Unique* members puberty has proceeded normally (Hubert 2006; Zollino 1995; *Unique*).

“ Very moody for two years, now thankfully she has grown into a very loving, caring lady ”

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

Delay in reaching the developmental ‘milestones’ of sitting, becoming mobile and walking is typical. Your baby will make progress, generally following the normal developmental sequence, but progress will come slower than for other children. How much slower depends chiefly on your baby’s innate abilities, but also on opportunities, on stimulation and to some extent on therapeutic interventions. It is hard to predict eventual mobility, but while in some it is normal, others may need a wheelchair.

From *Unique*’s experience, babies learned to roll over between seven and 26 months, to sit without support between six and 28 months, to become mobile between nine months and three years and to walk between 13 months and four years six months. Not all babies crawled: some shuffled on their bottoms or rolled over and over, while others crawled backwards. Walking may remain unsteady for a long while after it is first achieved and your child may walk with their feet wide apart to improve their balance. A buggy may be needed for outdoors or for long expeditions for a long while. Once on their feet, some children rapidly acquire skills such as running, skipping and hopping, but this is not possible for all.

“ At the age of 7, he runs and walks in a typical way with no supports or aids ” - *4q27qter duplication*

“ She needed physiotherapy to achieve the usual milestones and at 11, has problems with stairs and escalators, finding them hard to get on and off ” - *4q25q31 duplication*

“ She walks OK but needs a wheelchair if her back and hips ache. She used to be able to walk a good distance but not at the age of 19, and needs a wheelchair ” - *4q28.3qter duplication*

“ Both I and my daughter have locked, painful knees and she has been diagnosed with arthritis for which she does exercises and wears insoles ” - *mother and daughter, 4q31.3q33 duplication*

“ He always seems quite stiff – particularly when getting up or getting down to the floor. But he is otherwise very mobile – loves dancing, playing soccer and cricket, riding his scooter and jumping on the trampoline. He currently has 1-2 hospital visits each year for Botox injections in his legs in treatment for his cerebral palsy ” - *4q28q35 duplication*

One of the causes of the delay in mobility is a low muscle tone (hypotonia). This makes a child or baby feel floppy to handle and generally improves and may resolve with physiotherapy and exercises. In some children, muscle tone increases, so that muscles remain unable to stretch. If this gives rise to toe-walking, a surgical intervention known as heel-cord lengthening may improve your child’s gait.

Spinal curve (scoliosis)

A small minority of youngsters (4/43) have developed a spinal curvature, in at least one case requiring surgery to fuse the vertebrae to keep the back straight (Hubert 2006; Fryns 1980; *Unique*). A slight curve may correct itself in time but progressive scoliosis can lead to problems sitting and if severe can cause heart and lung problems. Treatment depends on severity and progression but may involve wearing a brace and surgery.