

Support and Information



Understanding Chromosome & Gene Disorders

Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

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Chromosome 6 research project

The C6 project works with families to collect detailed information with the aim of linking specific disease characteristics with specific regions of chromosome 6.

<https://www.chromosome6.org/>

Facebook page for chromosome 6

www.facebook.com/groups/chromosome6

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.

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick and by Dr Christiane Zweier, Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Germany, 2010.

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Understanding Chromosome & Gene Disorders

Duplications of 6q



rarechromo.org

Children with different duplications



6q11-13



6q13-15



6q13-q16.2



6q23.3-q25.3



6q24.1-q26

Sources and references

The information in this guide is drawn from what is known about around 47 babies, children and adults with a duplication of part of the long arm of chromosome 6, aged between birth and 55 years. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain articles from *Unique*. The leaflet also draws on *Unique*'s database. (Zweier 2008; Pazooki 2007; Valerio 2006; Ness 2002; Causio 2001; Cappon 2000; Smith 1999; Conrad 1998; Pratt 1998; Zneimer 1998; Arthur 1997; Henegariu 1997; Temple 1996; Giardino 1994; Brøndum-Nielsen 1993; Ohta 1993; Roland 1993; Smith 1991; Pivnick 1990; Taysi 1983; Stamberg 1981; Turleau 1981; Chen 1976; *Unique*)

Sometimes a relevant change is found in one parent's chromosomes. This is usually a rearrangement known as a balanced translocation in which material has swapped places between two different chromosomes. As no genetically important material has been lost or gained, the parent usually has no health or development problems, although they may have experienced difficulties with fertility. There are two main types of balanced translocation.

One type is called a balanced insertional translocation. A parent with certain balanced insertional translocations has an increased risk of having a child with a duplication or with a deletion. The other type is called a balanced reciprocal translocation. A parent with certain balanced reciprocal translocations has an increased risk of having a child with a duplication and a deletion. When this occurs, it is known as an unbalanced translocation.

Occasionally, the same duplication in a child is found in one of their parents as well. If one parent has the same duplication, it has been inherited.

If one person in a family with a 6q duplication 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. (Pazooki 2007; Roland 1993)

Can it happen again?

In families where both parents have been tested and have normal chromosomes, the risk of having another child with a 6q duplication is hardly any higher than anyone else's. In families where one parent has a balanced translocation or another relevant change in their chromosomes, there is an increased risk of having further affected pregnancies. In families where the 6q duplication has been inherited from a parent, the possibility of having another child with the 6q duplication rises to as much as 50 per cent in each pregnancy. The effect of the duplication on the child cannot be reliably predicted, however.

If they wish, parents should have the opportunity to meet a clinical geneticist or 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 very accurate, although not all of these tests are available in all parts of the world.

Will my child with a 6q duplication have similarly affected children?

Some children with a 6q duplication may eventually want to have children of their own. Not enough is known to be certain if it affects fertility but in some cases fertility may well be normal. In each pregnancy, someone with the duplication 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 their own learning ability. (Pazooki 2007; Roland 1993)

looking, her hands and her arms. Like everyone with a disability she is very special, above all for her parents and sisters. She always shows us that despite the difficulties you can go on and feel really happy. Just having her close, hearing her sounds and laughs makes you feel better. We are very proud of her little steps forward and she teaches us to play things down and attach importance to just the things that are really important. For us, it is like having an angel close to you every single moment - *6q13q15 duplication at 14 years*

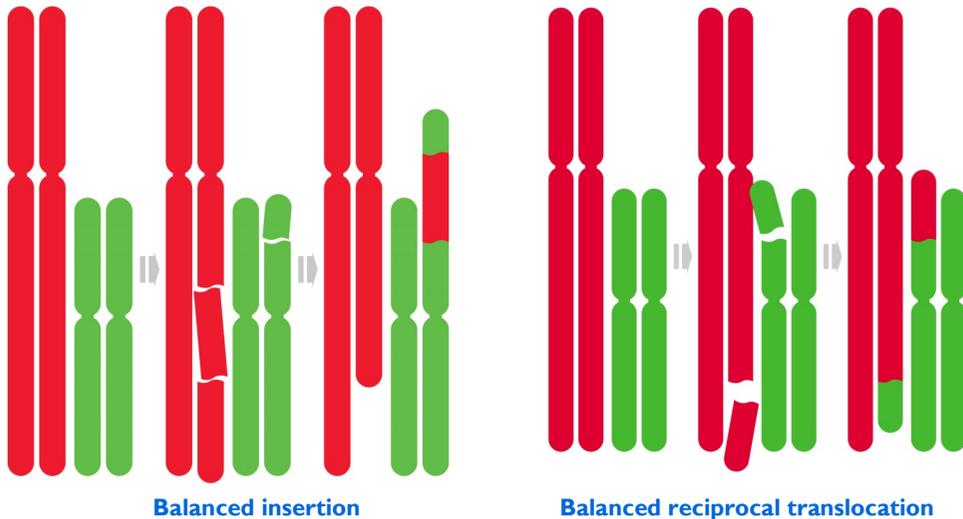
“ He is a very happy, content child. He is friendly and greets people. He does prefer to interact with those who he knows but is very friendly. When he feels stress he talks too loudly and yells. We try to keep his anxiety to a minimum - *6q21q23.3 duplication at 14 years*

How did the 6q duplication happen?

A 6q duplication can occur out of the blue for no obvious reason or it can occur as a result of a change in either the mother or the father's chromosomes. The only way to find out is to check the chromosomes of both parents. The parents' chromosomes should be checked even if they are themselves completely healthy with no developmental problems at all.

If no relevant changes are found in either parent's chromosomes, the duplication is said to have occurred *de novo*, meaning a new event – see page 4/5. *De novo* changes usually occurred well before the baby was conceived when the parents' sperm or egg cells were formed. They are no-one's fault. There is nothing a parent could have done to cause the chromosome change and nothing they could have done to prevent it occurring in their baby. No environmental, workplace, dietary or lifestyle factors are known to cause these chromosome changes.

Two different types of balanced translocation



What is a 6q duplication?

A 6q duplication is a rare genetic condition caused by an extra piece of one of the body's 46 chromosomes.

What are chromosomes?

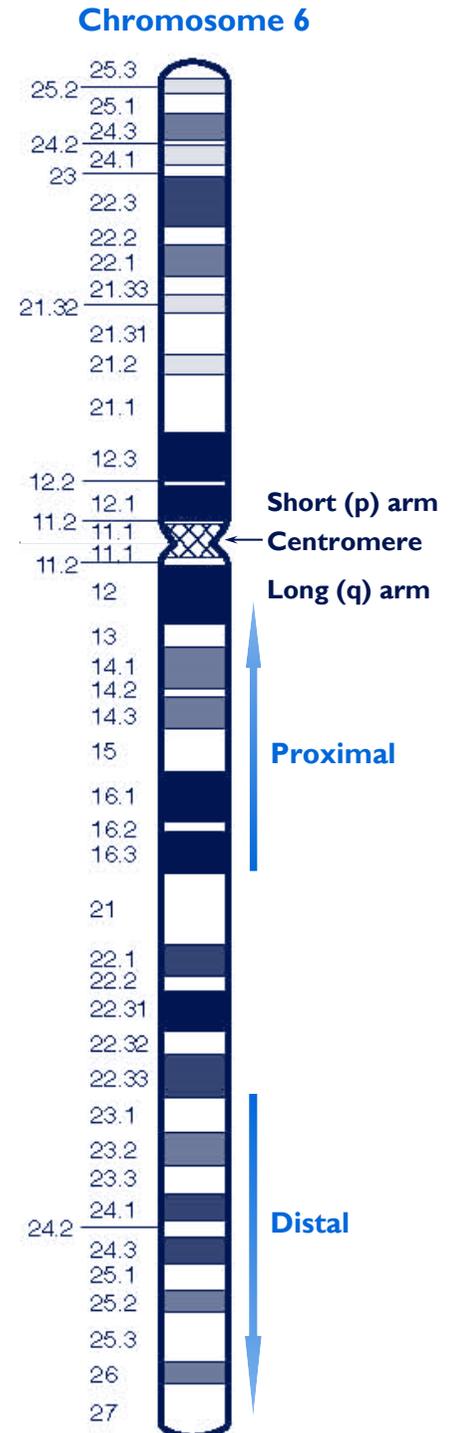
Chromosomes are the structures in each of the body's cells that carry the genetic information that tells the body how to develop and function. Apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy), they are numbered 1 to 22, approximately from largest to smallest. So chromosome 6 is one of the larger chromosomes. In the cells of the body, there are two of each of the numbered chromosomes, one that comes from the father and one from the mother. Each chromosome has a short (p) arm and a long (q) arm, as you can see in the diagram on the right.

For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. People with a duplication of 6q have one intact chromosome 6, but they also have an extra piece of the other chromosome 6. This is very likely to affect their learning and physical development. Chromosomes contain genes and most of the clinical difficulties that someone with a 6q duplication faces are likely to be caused by having an extra copy of a number of genes. However, a child's development, needs and achievements are also influenced by their other genes and personality.

Looking at chromosome 6q

Chromosome analysis

You can't see chromosomes with the naked eye, but if you stain them and magnify them many hundreds of times under a microscope, you can see that each one has a distinctive pattern of light and dark bands. In the diagram of



chromosome 6 on page 3 you can see that the bands are numbered outwards starting from the point where the short and long arms meet (the **centromere**).

Molecular techniques

If you magnify chromosome 6 about 850 times, it may be possible to see the extra piece of chromosome material. But sometimes the extra piece is so tiny that the chromosome looks normal down a microscope. The extra section can then only be found using more sensitive molecular techniques such as FISH (fluorescence in situ hybridisation, a technique that reveals the chromosomes in fluorescent colour), MLPA (multiplex ligation-dependent probe amplification) and/or microarray such as array-CGH or a SNP array, techniques that show gains and losses of tiny amounts of DNA throughout the chromosomes. Tiny losses and gains that cannot be seen through a microscope are called **microdeletions** and **microduplications**. A microarray is a new, particularly helpful technique that can show whether particular genes are present or not. Chromosome 6 contains between 1100 and 1600 genes.

Different types of duplication

The extra piece of 6q may run in the same direction as the rest of the chromosome. It is then called a **direct duplication**. If it runs in the opposite direction to the rest of the chromosome it is called an **inverted duplication**. The duplicated material may be incorporated into the long arm of chromosome 6. On the other hand, it may be inserted into a gap in any of the other chromosomes; it is then called an **insertion**. Look at page 22 for an example of an insertion.

Occasionally, the extra material may exist as a small, separate 47th chromosome. This type of chromosome is called a **marker** or a **supernumerary marker chromosome**.

In any of these arrangements, the main effects of the duplication will probably be caused by the extra genes in the duplicated piece.

Some people have extra material from one chromosome (6q) in the place of missing material from a different chromosome, as a result of two pieces of different chromosomes changing places. This arrangement is known as an **unbalanced translocation**. In people with an unbalanced translocation, there are usually effects both from the duplication and from the missing material (deletion). So people with an unbalanced translocation are not included in this information guide.

Results of the chromosome test

Your geneticist or genetic counsellor may give you your child's karyotype, a way of writing down what their chromosomes look like that shows the point/s where the chromosome has broken. It is likely to read something like this:

46,XX,dup(6)(q21q22.1)de novo

46 The total number of chromosomes in your child's cells
XX The two sex chromosomes, XY for males; XX for females
dup A duplication, or extra material. Other words that may appear here are **dir** (direct), meaning that the extra piece runs in the same direction as the rest of the long arm; or **inv** (inverted), meaning that the extra piece runs in the opposite direction

“ He is able to speak but has a device if he is unable to make himself understood. He started talking when he was 5 or 6 and now uses 2 to 4-word phrases - 6q21q25 duplication at 14 years

Behaviour

It is not yet known whether there is a typical behaviour pattern for children and adults with 6q duplications. Families generally describe their children as happy and sociable, especially when the focus of attention, but prone to problem behaviours when frustrated, anxious, jealous, tired and possibly also when bored. Problem behaviours can be quite severe and include restlessness, skin picking, biting, repetitive movements such as rocking, head banging, spitting and targeted aggression. This can mean that the child is very demanding. Families actively seek situations in which their child is relaxed and sociable, often enjoying 1:1 attention with an adult, and avoid situations that promote confusion and unresolvable anxiety.

Some children find body language hard to read and many do not respond as expected to pain. Overall, children may behave in some ways just like other children of their own age while in other ways they behave like a very much younger child. One child has been diagnosed with autism. While it is clear that others show behaviours within the autistic spectrum (especially repetitive movements), a formal diagnosis is not reached. Families facing persistent problem behaviours should seek advice and support from a behavioural therapist. (Zweier 2008; *Unique*)

“ He loves music and wants to use the computer all the time, is happiest with lots of people, very sociable, loves to be entertained, animals make him laugh uncontrollably. Socially he is very cute and sweet. He is also very demanding – 110% attention and devotion are needed to keep him happy. When entertained, he is adorable, funny and charming. But he can turn abusive to his mother and 3-year-old sister if she gets the attention and can have huge, long-lasting tantrums - 6q23.3q25.3 duplication at 2 years
“ He always loves to have background noise. He gets very frustrated and will go up to any stranger and try to take food etc. Socially, he can be quite rough but it's not always intentional: it's his way of displaying affection - 6q13q16.2 duplication at 3 years
“ A very happy child and a very calm girl; she doesn't get flustered, doesn't shout and doesn't convulse. She just has a repeated movement (stereotypy) while sitting, she moves herself forward and backward repeatedly, but just in certain circumstances, usually when she is tired, bored or even when she is going for a walk in places she recognises. She is very affectionate and has good interaction with people through



3 years

How can communication be affected?

Communication skills are generally delayed but there is very wide variation between individuals, with a spectrum ranging from some speaking in full sentences and singing from early childhood (albeit later than their brothers or sisters) to others who have limited and sometimes unclear speech and may restrict themselves to single words or monosyllables. As an adjunct, children use a wide variety of alternative means of communication, including tone, gesture, body language, facial expression, vocal noises, approximations and signing. The evidence from *Unique* suggests that most children with a 6q duplication do not need an assistive communication device but can take advantage of one if it is available.

The information available suggests that first words emerge any time from the age of 2 to 10 years and may develop later. Children usually understand more than they can express, especially when they are given maximum help using focused attention and short phrases and words are supplemented by body language and physical manipulation. Children and adults with small duplications between 6q21 and 6q23 generally appear to have better preserved communication skills than others and may be able to express themselves as well as anyone without a chromosome disorder. Apart from this, there is no obvious link between the precise 6q duplication and communication ability. (Zweier 2008; Pazooki 2007; Causio 2001; Smith 1999; Conrad 1998; Pratt 1998; Zneimer 1998; Giardino 1994; Brøndum-Nielsen 1993; Roland 1993; *Unique*)

“ In the last three months his understanding has been incredible: he understands a lot more now than he can express. He has about 8 words and copies some letter sounds. His words are not yet clear or understandable to others and he still has difficulties saying a lot of the letters: c,k,e,g,h,l,l,p,q,r,s,t,u,v,w,x and z - 6q23.3q25.3 duplication at 2 years

“ He is good at catching the last word of the sentence - 6q14.3 microduplication at 7 years

“ She communicates with gestures, sounds and words. She understands many verbal commands, follows stories and cartoons although we do not know how far she understands the point of the story. She interprets situations in her visual diary very well, behaves well at school, taking turns, joining in when it is her turn, keeping quiet when required. She can repeat sounds such as a, o, u, k, t, m and p. She says a few words: mama, shoe etc, and the names of some of her friends and uses a wide repertoire of around 50 gestures. She also recognises onomatopoeic animal and other noises - 6q24.1q26 duplication at 7 years

“ She cannot speak but can communicate with monosyllables, sounds and her smile. It is easy to recognise that she is sad, because she cries or gets serious; and also when she is happy, because she smiles and laughs easily. She understands simple orders, like ‘Let’s eat!’, ‘Let’s go outside!’, or ‘Let’s go to bed!’. She agrees by nodding; she communicates refusal by moving her hands and crying - 6q13q15 duplication at 14 years

“ He uses speech, signing and the written word. His expression has improved with the use of sign for clarity. He does speak in sentences but does not always hold a conversation with unknown people if he doesn’t want to. His speech is sometimes unclear due to his hearing loss - 6q21q23.3 duplication at 14 years

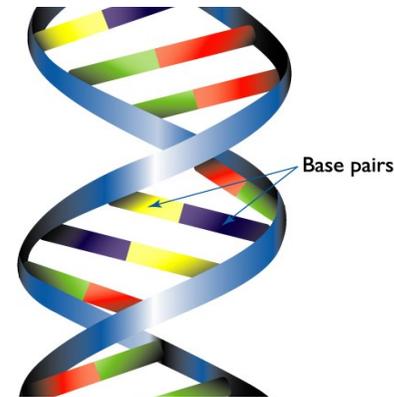
- (6) The duplication consists of material from chromosome 6
(q21q22.1) The chromosome has broken in two places, one in band 6q21 and the other in 6q22.1, indicating a small duplication
- de novo The parents’ chromosomes have been checked and no rearrangement found involving 6q. The disorder is then very unlikely to be inherited and has occurred for the first time in this family with this child.

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

arr 6q24.1q25.3(142792084-157540752)x3

- arr The analysis was by microarrays
6q24.1q25.3 (142792084-157540752)x3 The analysis revealed a duplication from band 6q24.1 to 6q25.3 Three copies of the piece of the chromosome between base pair 142792084 (in 6q24.1) and base pair 157540752 (in 6q25.3) were found instead of the expected two copies. The first number is the start of the duplication; the second is the end of the duplication; the difference between them is the number of extra base pairs.

In the picture below, the medium-blue strands are DNA. The base pairs are the chemicals in the DNA that form the ends of the ‘rungs’ of its ladder-like structure. Counting the base pairs gives a measure of the length of DNA. Chromosome 6 has around 171 million base pairs. That is usually written 171 Mb. Genes in humans vary in size from a few hundred base pairs to more than two million base pairs.



bp 1 base pair
kb A thousand base pairs
Mb A million base pairs

Are there people with a 6q duplication who have developed normally and have no health, learning or behaviour difficulties?

Some people are quite mildly affected by a duplication of 6q, in others it has a more marked effect. Where the duplication is small and consists of material from bands 6q21 to 6q23, the effects can be fairly mild. In at least one adult, a chromosome disorder was not suspected and analysis was only undertaken after a 6q duplication was found in her daughter. The mother had the same duplication (6q21q22.1) as her daughter and was working as a hospital assistant (Pazooki 2007). In two further cases where development was reported to be normal, children were still very young when they were assessed (17 months, duplication of 6q21q22 and two years, duplication of 6q22q23). (Valerio 2006; Arthur 1997)

Most likely features

- Some effect on development and learning ability
- Unusual facial features for the family
- Transient neonatal diabetes mellitus
- Small head
- Unusual genital features, typically in boys
- Unusual features of the kidneys, bladder and urine collection system
- Tightly bent joints
- Slow growth, in some cases starting in the womb before birth
- Brain anomalies
- Heart anomalies



A feeding tube need not stop life being fun

Some effect on development and learning ability

Children will usually need some support with their learning, but the amount of support they need varies hugely - from children with only mild or possibly no delay to others with profound learning disabilities. In all, 34 out of 36 children and adults with a 6q duplication have experienced developmental delay, learning disabilities or both.

Two children who apparently had no delay were both very young when they were tested (17 months and two years). An adult woman of 55 had educational problems at school but was working as a hospital assistant and was the mother of three children. (Pazooki 2007; Valerio 2006; Arthur 1997)

Development and learning: Relatively mild difficulties

It seems that children and adults with duplications between bands 6q21 and 6q23 can have relatively mild developmental delay and learning difficulties. The 17-month-old and two-year-old toddlers mentioned above with apparently normal development have a 6q21q22 duplication and a 6q22q23 duplication respectively; the adult referred to in the previous paragraph has a duplication of 6q21q22.1, as has her daughter, who at 10 years 11 months had a developmental age of 6 years 9 months. A five-year-old girl with a 6q21q23 duplication was at a 19-month developmental level at 28 months; and a 7-year-old girl with a 6q21.1q23.3 duplication has a 'mild' learning disability. A *Unique* member with a 6q21q23.3 duplication is reading and writing at third-grade level (age 8-9) at the age of 14. He can read simple books, signs or words on television or the computer. He copes well with a computer and with video games. He can do simple sums and loves to draw people and cartoon characters. He can write simple sentences and signs (overall IQ 63; verbal IQ 81; performance IQ 60).

Nonetheless, development is uneven: a 5-year-old with a 6q21q22.1 duplication is not toilet-trained; a child with a 6q21q23.3 duplication was successfully toilet-trained at 13. (Pazooki 2007; Valerio 2006; Pratt 1998; Zneimer 1998; Arthur 1997; *Unique*)

“ He is enrolled in special education in our local public school system with the services of an interpreter almost all of the time, attending mainstream woodshop and art. His interpreter keeps him on task and helps him to understand directions. His favorite

“ He had hypotonia as a baby but did daily exercises under the guidance of a physiotherapist and was walking on his own at two and a half - 6q13q16.2 duplication
“ His mobility is excellent now - 6q21q25 duplication at 14 years



13 years

Feet

Although most babies with a 6q duplication are born with normal, flexible feet, there is a tendency for those with a duplication between 6q21 and 6q23.3 to be born with clubfoot affecting one or both feet. Babies with duplications of other bands of 6q have also been born with a clubfoot or fixed contractures of the ankles. The foot may be inflexible and fixed, needing surgery to correct its position; or the joint can be movable. Treatment is individually tailored and aims to straighten the foot so that it can grow and develop normally. First-line treatment is usually non-surgical and may include manipulation, casting, taping, physiotherapy and splinting, followed by bracing to prevent relapse. Surgery and sometimes splinting are considered if non-surgical treatments are not completely successful. (Zweier 2008; Ness 2002; Smith 1991; Pivnick 1990; Stamberg 1981; *Unique*)

Around one baby in 10 is born with extremely small feet. This usually matters only if the feet are so small as to interfere with balance, when shoes with externally stitched soles can be chosen. (Zweier 2008; Smith 1999; Pratt 1998; *Unique*)

Other unusual features seen occasionally are webbing between the toes (especially toes 2 and 3); flat feet; and among those with a more distal duplication, contracted joints within the foot. (Zweier 2008; Henegariu 1997; Giardino 1994; Brøndum-Nielsen 1993; Roland 1993; *Unique*)

“ He has very small feet that are very slow to grow. We have orthotics (supports) as his feet and ankles roll in and his toes are badly curled to the point that he walks on his toenails - 6q13q16.2 duplication at 3 years

Sitting, moving: gross motor skills

The great majority of babies and children with a 6q duplication do learn to walk independently. The early stages of whole body control, such as head control and sitting alone, are typically delayed but with maturity, practice and physiotherapy children reach other developmental milestones - usually a little late but sometimes within normal limits for children without a chromosome disorder.

Muscle tone is affected by the chromosome disorder in a significant number of babies. Among those with a proximal duplication, a low muscle tone (hypotonia) is sometimes found, making a baby feel floppy to hold and increasing the effort needed to achieve positions such as sitting and standing. In addition to regular physiotherapy and sometimes special clothing to support the upper body, families of other hypotonic babies have experimented with taping the trunk to promote stability. Some children need walking aids and supportive footwear. Among children with a distal duplication, a raised muscle tone is more often found (hypertonia), so that limbs may be unnaturally stiff and require regular stretching exercises under the guidance of a physiotherapist.



6 years

The contracted joints that are typical for babies with a distal duplication (see page 11) have an obvious impact on mobility. A physiotherapist will combine approaches to improve a child's mobility most effectively.

Evidence from *Unique* and the medical literature shows that babies with a proximal duplication learned to sit between 10 and 12 months and to walk between 16 months and 3 years. Once sitting independently, babies may lack a 'save' reflex, so need seating in safe surroundings. Children may become mobile, some by conventional crawling but others using ingenious alternatives including commando crawling (creeping), bottom shuffling (scooting), spinning or continuous rolling. Those with a 6q21q23 duplication were generally walking by

their second or third year while those with a more distal duplication sometimes became mobile later than this. (Zweier 2008; Pazooki 2007; Causio 2001; Smith 1999; Conrad 1998; Pratt 1998; Arthur 1997; Henegariu 1997; Brøndum-Nielsen 1993; Roland 1993; Turleau 1981; Chen 1976; *Unique*)

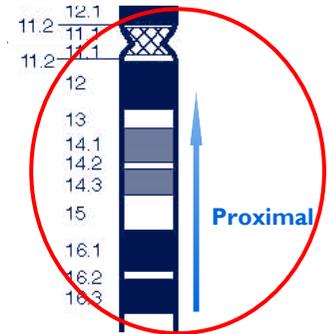
“ Every stage is reversed: he could walk when he was 22 months, then he sat up by himself and started crawling - *microduplication at 6q14.3*

“ He was climbing stairs by two and a half and needed no supports or aids - *6q11q13 duplication*

activities are currently Nintendo and Wii games and he plays computer games too. He acts out TV and games characters in play alone and with others; his favorites are action figures from TV who he also likes to draw. But he is still not good with buttons or tying shoes and does require some help to have it done well. It does take him longer to dress and we use elastic waist trousers - *6q21q23.3 duplication at 14 years*

Development and learning: Duplications of the top parts of chromosome 6q (proximal duplications)

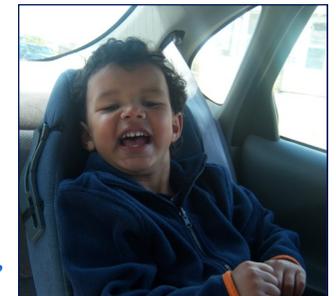
Children with duplications of parts of the top of the long arm (roughly speaking between bands 6q11 and 6q16) appear to need a moderate to significant amount of support with their learning. Reading and writing may be possible to some extent for some, but the main focus of learning is likely to be on skills needed for daily living and children are likely to continue to need help with these skills into adulthood. Some children need very significant amounts of support with daily tasks such as washing, dressing and toileting and evidence from *Unique* suggests that they find the fine motor skills (hand-eye coordination) needed for even limited independence very difficult to master. But people with exactly the same duplication can develop differently, even in the same family. In one family, three sisters all have a duplication of 6q14 to 6q16: while one sister has moderate to severe learning disabilities, the other sisters are mildly to moderately affected. (Roland 1993; *Unique*)



“ He is just starting very primitive painting but he still loves to mouth everything, including paintbrushes. We have attended an Early Intervention Centre from four months of age and he attends a crèche with a 1:1 carer two days a week for socialisation. Next year he will go to a special developmental school. He loves wiggles and music, playing ball and cars - *6q13q16.2 duplication at 3 years*

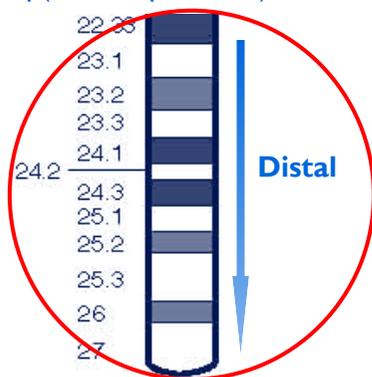
“ She enjoys going for a walk, going to the swimming pool, hearing human voices (above all singing), being played with and having baths at home. She goes every day to a special needs school and is in the basic level there. Her learning disabilities are very severe - *6q13q15 duplication at 14 years*

“ He recognises all the upper case letters of the alphabet, but some in the lower case are a bit difficult. He counts from 1 to 10. He is good at music pitch and good at using a computer. He remembers all the icons on the desktop, and is good at finding different links leading to his favorite videos. He learns best when his teachers are nice and gentle with him. Reading, drawing and writing are still difficult for him but he is very good at using the computer keyboard. He goes to a special education class in a regular school and most enjoys playground, gym, computer and music - *6q14.3 microduplication at 7 years*



6q11q13: 3 years 11 months

Development and learning: Duplications of the bottom parts of chromosome 6q (distal duplications)



Children with duplications of parts of the bottom of the long arm (roughly speaking between band 6q23 and the end) appear to need a moderate amount of support with their learning, but some will need more, especially when they have a particularly large duplication. Reading and writing may well be possible for some, but as with children with a proximal duplication, a key focus of learning is likely to be skills needed for daily living. Reports of severe to profound developmental delay and learning disabilities occur in reports in the medical literature from a generation or more ago.

A 12-year-old boy with a duplication from 6q23 and developmental delay obvious from the age of three months has 'prominent' learning difficulties; a child with a duplication from 6q24/5 appeared at birth to be severely affected but improved with time and needs a moderate level of support. A 14-year-old girl with a 6q24.1q25.3 duplication has 'simple reading and writing abilities' and is described as mildly to moderately retarded. A nine-year-old with a duplication of two bands of 6q24 is reading but not writing well. A seven-year-old with a duplication of bands 6q24.1 to 6q26 is considered by doctors to have moderate to severe learning difficulties and according to her mother is like a 1-2 year old child, but with a much broader experience of life. (Zweier 2008; Ness 2002; Causio 2001; Smith 1999; Conrad 1998; Brøndum-Nielsen 1993; Turleau 1981; Chen 1976; *Unique*)

- “ He has just started feeding himself with a spoon and can try to brush his teeth. He helps put his arms through sleeves and legs through his trousers when dressing. He still needs a lot of help with everything but is determined to try too - 6q23.3q25.3 duplication at 2 years
- “ She isn't good at memory games, but remembers well the names of dogs or children she knows. Taking part in a group activity is a good way to get her to learn, as well as repeating what others say - 6q24.1q26 duplication at 7 years
- “ He has been home schooled from age 6 and has seven teachers who work with him. He now reads level one books and draws and writes at 1st grade (age 6) level. He enjoys the computer, Barney, the Disney channel and DVDs, shopping at local foodstores, going out to eat, flying, staying at a hotel and he loves his dog. He has trouble holding cutlery, holding his hands flat and opening a bottle; he is unable to ride a bike or wash or comb his hair. But he is able to brush his teeth and dress himself although his clothes go on backwards - 6q21q25 duplication at 14 years

Children benefit from early intervention programmes and from attending special pre-schools and schools where their individual needs can be met properly. It is to be expected that they will have a learning support statement or plan. Depending on local provision, they are likely to attend a school attended by other children with special learning or physical needs or in some cases a mainstream (regular) school.

What about food and eating?

Feeding and eating problems occur in some but certainly not all babies and children. A few babies breastfeed successfully but others do not manage to latch on to the breast or to suck and/or swallow effectively. Others have little appetite and need to be woken for feeds. In some cases feeding problems ease after the neonatal period but other babies benefit from a period of feeding via a nasogastric tube threaded up the nose and down the throat. Some babies continue to choke as they feed, particularly when swallowing liquids.

While some children move on to solids at the expected age and cope better with solids than liquids, many are late in weaning and need their food processing or cutting up small for a long time.

Gastro-oesophageal reflux and vomiting are common, with a risk of aspiration pneumonia. Reflux may resolve once milk feeding is over or may persist. Careful feeding, using feed thickeners and medications prescribed to inhibit gastric acid, can control reflux in some babies. If not, an operation called a fundoplication can improve the function of the valve from the stomach to the food passage. Babies may need to be fed by tube when they are ill and it is sometimes necessary to insert a gastrostomy tube for direct feeding to the stomach.

If feeding and eating delays become persistent, input from a speech therapist expert in feeding and possibly from a psychologist with experience of feeding difficulties can help to overcome longstanding problems. (Smith 1999; Conrad 1998; Brøndum-Nielsen 1993; Taysi 1983; Chen 1976; *Unique*)



2 years

- “ I tried to breastfeed but could not attach – he had a very poor sucking and swallow reflex. We attended many clinics to try and teach him to breastfeed but were not successful. I expressed for 8 months and fed him with a Haberman teat (designed for babies with special needs), then went to teats designed for cleft palates, then on to a cup with a cross-cut teat with formula. Now he is three and a half, he still has a very low consumption of liquids but tolerates all types of food and solids and has recently learned to feed himself with a spoon - 6q13q16.2 duplication
- “ No problems with breast feeding. He gained weight quickly and ate well and nursed until he was 18 months old. Textures bothered him a lot so he ate baby food for quite some time - 6q21q23.3 duplication
- “ At birth she had little energy to feed and great problems with releasing gas. For the first year of her life, she slept in our arms, since movement was the only way to calm her. We later tried a medicine that contains simethicone and this helped. For a number of years all her food was mashed. Today, at 7 years old, she eats only small pieces since she chews little. She finds vegetables especially gaseous and frequently chokes when drinking water - 6q24.1q26 duplication

Hearing

Children can usually hear well. However, like all young children, they are vulnerable to the temporary hearing loss caused by so-called glue ear, a build-up of fluid within the middle ear, frequently as a result of ear infections. This can usually be relieved by placing grommets (aeration tubes) in the eardrum. Sometimes extra steps are taken to improve drainage from the middle ear, such as removing the adenoids. If these measures do not improve hearing to useful levels, hearing aids will be considered. Just one child with a 6q duplication has been diagnosed with a severe hearing loss and it is not known whether this was temporary, caused by glue ear or delayed maturation of the hearing pathways in the brain. (Conrad 1998; *Unique*)

“ He has had recurrent otitis media with perforation and glue ear; he has had tubes fitted and been on multiple courses of antibiotics and is now on a long-term antibiotic and has had a remarkable improvement. His ear drums are both perforated and as a result he has hearing loss and wears aids. His hearing loss has fluctuated from mild to moderate, worse when he was younger due to fluid before the tubes but hopefully once we have the eardrums repaired his hearing will be normal - 6q13q16.2 duplication at 3 years

Teeth

Many children with a 6q duplication have strong, healthy teeth but generally speaking, children with chromosome disorders have a somewhat higher rate of unusual dental features than other children. Children and adults can resist having their teeth cleaned, especially when they do not associate mouthing with pleasure. Children may need specialist treatment in part because they can need a general anaesthetic for dental procedures.

Teeth may emerge early, late or in an unexpected order. They may be larger or smaller than usual and can have an odd shape. Milk teeth may not fall out in time to be replaced by adult teeth. Upper teeth may not align well with the lower teeth, especially when the lower jaw is small. Necessary medicines, such as antibiotics, can affect teeth as they are developing. (Zneimer 1998; *Unique*)

“ It’s hard going for check-ups: he dislikes having his teeth examined - 10 years

At birth



Among *Unique* members and others reported in the medical literature, there is no such thing as a typical 6q duplication baby at birth. Some babies are born small and light, while others have grown well in the womb and are a good size at birth. Some babies have physical anomalies, while others are perfectly formed. Some babies are quiet, others active. Apgar scores, a measure of wellbeing with a score out of 10, range from low to full marks. One or two babies need extra oxygen to support their breathing. One or two contract a serious infection shortly

after birth and need intensive care and some babies born early or particularly small spend many weeks in intensive care. Other problems noted among newborn babies are a low or high blood sugar (hypoglycaemia, hyperglycaemia - see page 10) and jaundice. (Ness 2002; Conrad 1998; Pratt 1998; Giardino 1994; Pivnick 1990; Taysi 1983; *Unique*)

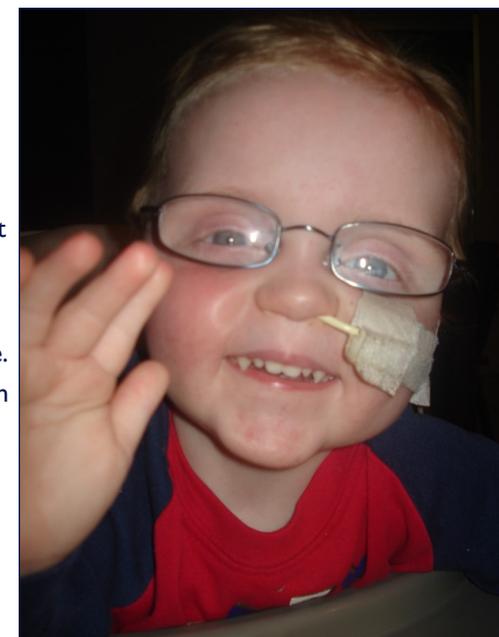
In common with others with a similar level of learning ability, children may well be late to show interest or curiosity in their surroundings, have a short attention span and require longer than normal to process information and project a response. Families say that their children learn best by repetition and individualised teaching, with familiar routines and consistency. Music, sensory play, and switch-operated and cause-and-effect toys are important aids to learning.

Hands

There is a tendency for children and adults with a 6q duplication to have small hands and short fingers. When the duplication is distal, long, tapering fingers are sometimes seen. More important from the functional point of view is that one or more fingers on either hand and joints such as the wrist may be bent and rigid at birth. In some cases joints can be straightened with regular massage and sometimes splinting, but this is not always possible.

Other features seen occasionally are an extra finger (and toe); and hands that are twisted outwards, towards the little finger. (Zweier 2008; Smith 1999; Conrad 1998; Giardino 1994; Brøndum-Nielsen 1993; Roland 1993; Smith 1991; Taysi 1983; Stamberg 1981; Chen 1976; *Unique*)

“ As an infant his hands were fistled for some time, so I had to do a lot of massage to get them to open up



2 years

Unusual facial features for the family

Many children and adults with a duplication of 6q look slightly different facially from other members of their family. They may have one or two unusual features such as eyes that are set wide apart and perhaps slant downwards. Among those with a duplication of material close to the end of the chromosome, a small or open, round mouth is quite common and some children and adults have a prominent forehead, while in others the eyes are slightly prominent. Among children and adults with a duplication of material from 6q21 to the end of the chromosome, a short neck is quite common, sometimes with extra skin known as webbing that makes it look broad. Other unusual facial features can include ears set low on the side of the head, tiny skin folds across the inner corners of the eyes (epicanthic folds), a small and perhaps upturned nose, thin lips, a large tongue, and a small and perhaps receding lower jaw. One child has small grey-white spots at the edge of the coloured part of the eye, known as Brushfield spots. Your child will not have all of these unusual features and is likely to have others all of



10 months

his/ her own as well as similarities with the rest of your family. One *Unique* member with a 6q23.3q25.3 duplication has reddish, very fine hair and very deep-set eyes; another has a 'Down syndrome look'; another with a 6q13q16.2 duplication has ear pits (tiny depressions just in front of the ears); and another with a 6q11q13 duplication has hooded eyelids.

Transient neonatal diabetes mellitus

Babies who inherit a particular gene known as *HYMAI* at 6q24.2 in duplicated material from their father are believed to be at risk of developing a high blood sugar in the first month of life. More specifically, the *HYMAI* gene is to be found between base pair 144324022 and base pair 144329866 on the long arm of chromosome 6. When two copies of the father's genes are present instead of one as is normal, it can cause the condition known as transient neonatal diabetes mellitus (TNDM). TNDM itself disrupts normal insulin secretion, causing slow growth before birth, small size at birth, dehydration and failure to grow well after birth. TNDM is controllable with insulin. In around half of all affected babies, TNDM lasts for two or three months before resolving spontaneously; in the others, it persists. In a significant number of people, insulin-resistant diabetes emerges later in life. (Cave 2000; Arthur 1997; Temple 1996; Brøndum-Nielsen 1993; *Unique*)

Small head

Your child's head may be very small. On growth charts, the circumference may be plotted below the lowest curve printed on the chart. Overall, around half of babies, children and adults with a 6q duplication have a very small head (microcephaly); others have average or even large heads. A small head is especially likely if your baby or child has a duplication close to the centromere (a proximal duplication) but children with other duplications sometimes also have a small head.

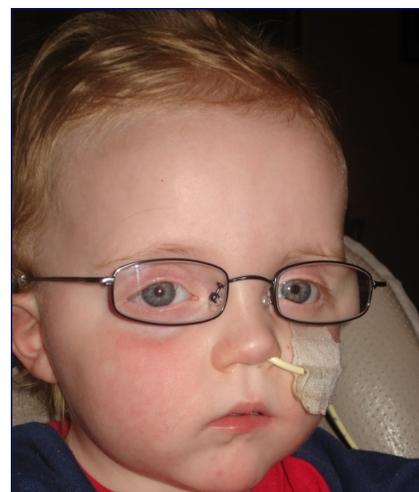
A small head indicates a small brain and while in some children this may not matter at all, in others the growth of the brain may have been affected. This is more likely if there is a genetic cause such as a chromosome disorder and children often have developmental delays and disabilities.

but in this case included corticosteroids to suppress the immune response and a blood transfusion to replace red blood cells.

A 4 year old with a 6q21 duplication has cyclical vomiting syndrome, where she has recurrent bouts of being sick (vomiting) and feeling tired and nauseated (sick) without any obvious cause. A 7-year-old with a 6q24.1q26 duplication has had two urinary tract infections and is awaiting an investigation of the function of her kidneys. Her blood sugar levels drop fast when she is unwell and unable to eat or drink, causing hypoglycaemia. After 24 hours of intravenous feeding she gradually starts to feed normally again. A baby with a 6q26q27 duplication was diagnosed with a low level of thyroid hormone, and treated with replacement therapy. (Brøndum-Nielsen 1993; *Unique*)

Eyesight

Most children and adults with a 6q duplication have entirely normal vision. Less than a quarter have some visual defect and this is usually one that is common in the general population and is simply corrected with glasses or surgery. Six children have strabismus (a squint), affecting one or both eyes. 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. Three children have notably long sight, correctable with glasses so long as the child finds them comfortable and useful enough to wear.



2 years



2 months

Other vision problems have only been observed once in this group and so can't be ascribed to the chromosome disorder. One child was observed to have a cataract on one eye (an opaque area over the lens) and roving eye movements; another child is extremely sensitive to sunlight; another child has developed a membrane over each eye caused by failure to close the eyes while asleep; another was born with glaucoma, where the optic nerve is damaged at the point where it leaves the eye. The cause may be raised eye pressure, a weakness in the optic nerve or both; treatment depends on the cause and some loss of vision may occur. (Pazooki 2007; Causio 2001; Conrad 1998; Brøndum-Nielsen 1993; *Unique*)

Heart problems diagnosed in individual children may be single or multiple. They include:

Patent ductus arteriosus – a channel known as the ductus arteriosus is a normal short cut in the circulation of the unborn baby. The channel usually closes naturally soon after birth. When it stays open, the lungs receive more blood than they should and the heart has to work too hard. It can be closed using minimally invasive surgery by inserting a coil via an artery in the thigh or it can be clipped or tied shut.

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

Ventricular septal defects (VSDs) - holes in the wall between the two pumping chambers of the heart (ventricles). This allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Treatment is determined individually. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from extra blood flow.

Aortic valve abnormalities - the aortic valve regulates blood flow from the left ventricle into the aorta, the blood vessel leading to the body. The valve may be weakened or inefficient, causing blood to flow back into the left ventricle of the heart. The valve normally has three flaps or valves, but a bicuspid valve has only two. In many cases no treatment is needed but a valve replacement may be needed.

Respiratory infections

Generally speaking, babies are vulnerable to respiratory infections in their early months and years and those with a 6q duplication are no exception. What is more, they do have additional risk factors. If they are taking food by mouth, they may swallow incorrectly and inhale some feed into their lungs, setting up a situation where aspiration pneumonia may develop. With careful feeding children generally outgrow this vulnerability although some develop asthma symptoms. Babies born with any unusual anatomical features affecting the airways may also have impeded breathing. One baby with a large duplication from 6q22 to the end of the chromosome was born with a partial blockage of the airways at the back of the nose (choanal stenosis); another child with noisy breathing had tissue near the voice box surgically reduced. A baby with a 6q21q23.3 duplication had several episodes of pneumonia but by the age of 13 had outgrown these and was very healthy. (Pazooki 2007; Pratt 1998; Conrad 1998; Taysi 1983; *Unique*)

Will my baby be healthy?

It isn't possible to give a definitive answer to this question but *Unique's* experience has been that most children do outgrow any early tendency to infections and become generally healthy children. Exceptions to this general rule include a child with a 6q13q16.2 duplication who developed autoimmune haemolytic anaemia when he was 2 years old. This is a type of anaemia where the body's immune system mistakenly attacks its own red blood cells, causing them to disintegrate. Treatment depends on the cause,

Unusual genital features, typically in boys

Minor genital anomalies are not uncommon in people with a chromosome disorder, especially boys and men. Around half of the males with a 6q duplication do have some minor genital anomaly, most commonly one or both testicles that are not yet descended at birth (cryptorchidism). In a few males, the hole usually at the end of the penis is sited on the underside instead (hypospadias) and the penis itself can be small. Occasionally, the penis may be buried within the pouch that contains the testicles (shawl scrotum) or within a fat pad.

There is only one report of a more significant problem, where a baby boy with a very large duplication from band 6q21 to the end of the chromosome was born with a female appearance of the genitals.

There is no obvious link between specific parts of 6q and these anomalies. Both hypospadias and undescended testicles can be corrected surgically, if need be, with minor surgery. (Smith 1999; Conrad 1998; Pratt 1998; Giardino 1994; Taysi 1983; Stamberg 1981; Turleau 1981; *Unique*)

Unusual features of the kidneys, bladder and urine collection system

Most babies with a 6q duplication are born with normal healthy kidneys and a well-functioning urine collection system. Four of the 47 people reported with a 6q duplication are known to have some unusual feature of the kidneys, the urine collecting system or the bladder. No anomaly appeared to result from the duplication of any particular gene or part of the chromosome. Two babies were born with small kidneys, which worked well. One baby with a large duplication from 6q21 to the end of the chromosome was born with one enlarged kidney and a 14-year-old boy was born with an unspecified abnormality of the urine collection system. Surgical correction of anomalies such as these is possible and quite commonly carried out. (Conrad 1998; Giardino 1994; Stamberg 1981; *Unique*)

Tightly bent joints

Among babies with duplications from band 6q22.32 to the end of the chromosome, it is common to be born with a number of tightly contracted, bent joints. Wrists, elbows, hips and knees can be most obviously affected, but any joints in the body can be unusually rigid. Regular physiotherapy will be needed, with stretching exercises to keep the joints moving and to increase their suppleness and range of movement. This may not be enough to gain a full range of function and surgery may be an option. (Zweier 2008; Ness 2002; Causio 2001; Conrad 1998; Henegariu 1997; Pivnick 1990; Chen 1976; *Unique*)

Slow growth, in some cases starting in the womb before birth

There is a tendency for children and adults with a 6q duplication to be short compared with others of their age. Around half of them are unusually short, regardless of the position or size of the duplicated material.

The unusually slow growth can start in the womb and be the first sign that the baby has a chromosome disorder. Around half of babies with a duplication of material between band 6q21 and the tip of the chromosome are small for dates during pregnancy and some of the other babies are smaller than average. Among babies with a duplication of material closer to the centromere it is much less common to be born small.

But the link being small at birth and short later on is not simple: some small babies grow into short adults while others catch up. By contrast, some average-length babies grow unusually slowly and become short adults while others grow into adults who are average or even tall.

And while some children and adults are plump and even overweight, others are skinny. It seems that while the 6q duplication makes it more likely that a child will be short, it doesn't define a child's rate of growth.



5 years

“ He’s tall (75th centile) with a slim build - 6q23.3q25.3 duplication, 2 years

“ He has always been on the shorter side, tracking along the 10th and sometimes up to 25th centile on our health records but has now dropped down to the 3rd centile.

He seems to have quite short legs, however, and is quite stocky with weight just on the 50th centile - 6q13q16.2 duplication, 3 years

“ He is like a 7-year-old, skinny and much taller than others of his age - 6q11q13 duplication, 5 years

“ She is 140 cm (4’ 7”) tall and weighs 29 kg (about 4.5 stone). She has always been under the weight and height average corresponding to her chronological age - 6q13q15 duplication, 14 years

“ Very short for his age. He weighs what he should for his age but is heavy because he is short - 6q21q23.3 duplication, 14 years

“ He’s estimated to grow to 5’4”(163 cm) - 6q25q21 duplication, 14 years

Brain

Structural or functional brain anomalies can occur in 6q duplications and should be screened for (Conrad 1998). If you only look at children and adults with ‘pure’ duplications, most do not appear to have a structural brain defect. A small minority (8/35) do, but they are of varying types and no one anomaly seems to be typical. A child with a 6q11q13 duplication has a small cyst and a child with a 6q13q16.2 duplication has some occasional slowing on EEG (electroencephalogram, a recording of the electrical activity of the brain) that is sometimes seen in the general population and more often in children with brain function disturbance. A child with a 6q16.3q22.2 duplication was born with the build-up of fluid within the brain known as hydrocephalus and an Arnold-Chiari malformation, where parts of the brain and brainstem intrude into the spinal

canal. The hydrocephalus was drained with a shunt and the Arnold-Chiari malformation treated with surgery. A child with a 6q21q23.3 duplication had asymmetrical fluid-filled spaces (ventricles) within the brain and the broad band of nerve fibres that links the two sides of the brain (the corpus callosum) was not seen. There were also some calcium deposits in the brain, which can interfere with the way it works. A child with a 6q22.32qter duplication had subependymal cysts, which are common in the general population and not necessarily considered significant. A child with a 6q24.1q26 duplication was born with a delay in the process of insulating the nerve fibres (myelination) as well as colpocephaly, where the back parts of the ventricles are larger than normal because white matter has failed to develop or thicken. A child with a 6q24.1q25.3 duplication had slightly enlarged ventricles, in itself common and not necessarily important. (Zweier 2008; Conrad 1998; Pratt 1998; Stamberg 1981; Unique)

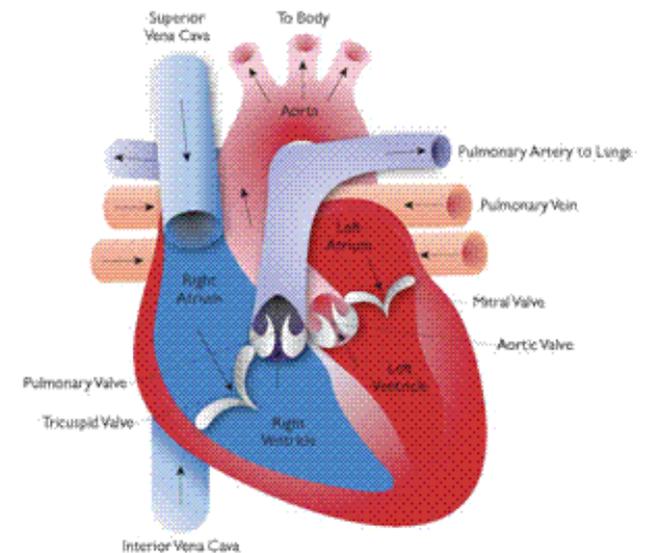
Heart

Structural heart problems are fairly common in babies born with a 6q duplication. It is unusual for babies with a proximal duplication to be affected (1/9) but among babies with a duplication of bands 6q21 or closer to the tip of the chromosome, 18/27 have a heart problem of some sort. Five babies or children have also been reported with an enlarged heart (cardiomegaly); if your child is affected, discuss with their heart doctor the possible causes and whether this is likely to affect the way the heart works.

Two babies have been diagnosed with right ventricular hypertrophy, in which the chamber is enlarged from which blood is pumped to the lungs to pick up oxygen.

Among the heart problems seen, the valves that regulate blood flow in and out of the different chambers of the heart are often affected. The valve may be inefficient, letting blood leak backwards or it may be narrow or even obstructed so that the heart has to pump extra hard for blood to pass through. The tricuspid valve usually has three flaps, but may only have two.

There may also be holes between the two lower chambers (ventricles) of the heart or, less commonly, between the upper chambers (atria). One child was born with an open ductus arteriosus, a normal feature of the circulation before birth. The ductus arteriosus channel was still open at the age of four years but she did not require surgery to close it. (Zweier 2008; Causio 2001; Conrad 1998; Pratt 1998; Zneimer 1998; Henegariu 1997; Giardino 1994; Smith 1991; Pivnick 1990; Taysi 1983; Stamberg 1981; Unique)



A normal heart