Understanding chromosome disorders

Unique

15q deletions

rarechromo.org

Sources and references

The information in this guide is drawn partly from the published medical literature.

The first-named author and publication date are given to allow you to look for the abstracts or articles on the internet in PubMed (http:www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from *Unique*.

The guide also draws on *Unique*'s database which contains information on how children and adults with chromosome disorders develop.

When this guide was written, *Unique* had 67 members with a pure 15q deletion not including the PWACR (Prader- Willi and Angelman critical region, see pages 3 and 4) or any other chromosome. Unique has many other members with the 15q11.2, 15q13.3, or15q24 microdeletion syndromes and has separate guides to these disorders. It also publishes a separate guide to 15q26 deletions.

15q deletions

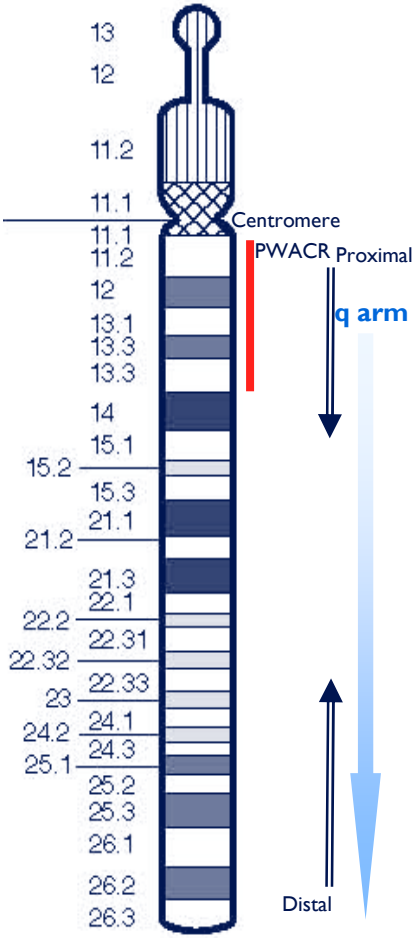
A chromosome 15q deletion is a rare genetic condition in which there is a missing copy of part of the genetic material that makes up one of the body's 46 chromosomes. Like most other chromosome disorders, this increases the risk of birth defects, developmental delay and learning difficulties. However, the problems that can develop depend very much on what genetic material is missing.

Chromosomes are the microscopically small structures in the nucleus of the body's cells that carry genetic information. Apart from the sex chromosomes (two Xs for a girl and an X and a Y for a boy), chromosomes are numbered from largest to smallest approximately according to size from number 1 to number 22. Chromosomes come in different sizes, each with a short (p) and a long (q) arm, so a 15q deletion means that material has been lost from the long arm.

The part of the arm that is close to the centromere, an important point where the short and long arms meet, is called the **proximal** part and when material is lost from this area it is called a proximal deletion. When the deletion is closer to the end of the chromosome, it is termed **distal**. Where there are two breakpoints that have rejoined, leaving a segment out, the deletion is called **interstitial**.

Where there is just one breakpoint before the end of the chromosome, the deletion is described as **terminal**, meaning that the end of the arm has been lost. Very small deletions from near the end of the arm of the chromosome are called **subtelomeric deletions**.

Your geneticist or genetic counsellor can tell you more about how much material has been lost. You will almost certainly be given a **karyotype**, a shorthand notation for your child's chromosome make-up, which will show the breakpoints in chromosome 15. Comparing your child's karyotype with others, both in the medical literature and within *Unique*, will help to build up a general picture of what to expect. But there will still be differences, sometimes quite marked, between your child and others with apparently similar karyotypes. It is very important to see your child as an individual and not to make direct comparisons with others with the same karyotype. After all, each of us is unique.



Chromosome 15

How did the deletion arise?

Some 15q deletions occur out of the blue. The genetic term for this is *de novo (dn)*. Others are the result of a rearrangement in one parent's chromosomes. A blood test to check the parents' chromosomes will show what the situation is.

De novo 15q deletions are caused by a mistake that occurs when the parents' sperm or egg cells are formed. When egg and sperm cells are formed, the two members of each pair of chromosomes normally line up together and then break and recombine to create new chromosomes that contain different combinations of the genes transmitted by the grandparents to the parents of the child. The recombining can occasionally take place between the wrong broken ends, and you can imagine how this could lead to a 15q deletion, but this is still a theory as nobody has ever seen it happen.

Recombining is part of a natural process and as a parent there is nothing you can do to change or control it. Children from all parts of the world and from all types of background have 15q deletions. No environmental, dietary or lifestyle factors are known to cause them. So there is nothing that either parent did before or during pregnancy that caused the deletion and equally nothing could have been done to prevent it.

Could it happen again?

The possibility that a couple will have another pregnancy affected by a 15q deletion depends on their chromosomes. If both parents have normal chromosomes, the 15q deletion in the child has in all probability occurred as a chance event, in which case the child's karyotype will be marked *de novo* or *dn*. It is then very unlikely to happen again.

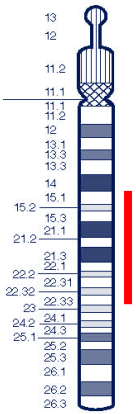
If a test shows that either parent has a chromosome rearrangement involving 15q, the chances of further affected pregnancies with similar or occasionally different abnormalities are high. Once the family translocation has been characterised, it will be possible to diagnose an unbalanced chromosome arrangement prenatally. Other family members should also be tested in case they, too, are carriers of the balanced form of the rearrangement. A clinical geneticist or genetic counsellor will give personal guidance.

Prader-Willi and Angelman syndromes

A child who has lost material from the proximal part of the long arm of chromosome 15, between 15q11 and 15q13, including a segment of the chromosome known as the PWACR - the Prader-Willi and Angelman Critical Region - is liable to develop one of two well-known syndromes. If the deletion has arisen on the chromosome 15 that came from the father, the child will have Prader-Willi syndrome, characterised by overweight, overeating, small genitalia in boys and men, low muscle tone and dysfunction of the central nervous system. If the deletion has arisen on the chromosome 15 that came from the mother, the child will have Angelman syndrome, characterised by developmental delay, speech delay or no speech, a movement and balance disorder, an excitable personality and inappropriately happy disposition. This leaflet does not cover these syndromes but more information for UK families can be found at

Prader-Willi Syndrome Association UK **www.pwsa.co.uk** 01332 365676
Suite 4.4 Litchurch Plaza, Litchurch Lane Derby DE24 8AA UK
Angelman Syndrome Support Education and Research Trust ASSERT
www.angelmanuk.org 0300 9990102
PO Box 4962 Nuneaton CV11 9FD UK

Unique publishes a separate guide to the 15q13.3 microdeletion syndrome



Interstitial deletions between 15q15 and 15q22

The red line shows roughly where the deletion is.
Pages with red bars by the page number are about interstitial 15q15q21/22deletions.

Some eleven cases with a pure deletion in this area are described, at least seven in the medical literature and five members of *Unique*, one of whom was also described in the medical literature. The oldest member of *Unique* was 16 years old when this information was compiled and the oldest person described in the medical literature was 22 years old. Within the group, there are five youngsters with a deletion of 15q15q21/q22 and six with a smaller deletion involving part of bands 15q21/q22 (Hutchinson 2003; Shur 2003; Koivisto 1999; Fukushima 1990; Martin 1990; Yip 1986; Fryns 1982; *Unique*).

Pregnancy and birth

There were some grounds for concern during **pregnancy** in all the cases with a larger deletion and some with a smaller deletion. Typically, too much amniotic fluid around the baby was noticed (polyhydramnios) or the baby was noted to be growing slowly and sometimes moving little. In one pregnancy, there was too little amniotic fluid around the baby (oligohydramnios) in the third trimester.

At birth

While most babies were light for dates at birth, this was not universal; one baby with a15q15.3q21.2 deletion weighed 4.025 kg (8lb 14oz), an above-average weight. The lowest birth weight at term was 2.070kg (4lb 9oz). Birth length was also variable, with some babies but not all shorter than average.

From the information available, it seems that most babies were not in very good condition at birth. Their Apgar scores (ratings of wellbeing at birth on a scale of 0-10) were usually low and sometimes very low. Some babies were floppy (hypotonic); typically they had difficulty feeding; and some had difficulty establishing breathing or stopped breathing for a spell (apnoeas) in the newborn period, and needed extra oxygen either short or longer term.

Appearance

In many cases, babies' heads were unusually small or an odd shape. As well as this, doctors may notice what are known as 'dysmorphic features' which may or may not be obvious to a parent. Most of these are facial features of little or no importance to the baby but they do help doctors to reach the correct diagnosis.

Some of the most common features seen include an unusually shaped nose, often beaked or prominent, with flat nostrils and an odd bridge; ears set below the line of the eyes, sometimes large or oddly shaped; a small or receding lower jaw and chin; a small mouth, sometimes held open, with a thin upper lip; arched eyebrows; a short neck; unusual skin, eye and hair colour compared with the rest of the family.

Hands and feet

Minor anomalies of the hands and feet are relatively common in children with chromosome disorders. These may just be cosmetic or they may make it harder for the child to use their hands or to walk. The most common feature affecting the hands in children with a 15q15q21/2 deletion include long and sometimes slender or tapering fingers. Among those with a smaller deletion, the hands may be small and even puffy and the fifth finger may curve inwards.

The feet may also be long, with long toes and there may be an overlap of toes 3, 4 and 5. The foot may be held in an odd position, turned inwards so that it needs correction with physiotherapy or surgery. In individual cases, the feet have been flat, with prominent heels or very broad big toes.

" It makes walking more difficult but he gets by. He's a fighter " - *15q21.1q22.3 deletion*

Feeding

The evidence from *Unique* is that babies have generally needed considerable support to establish effective feeding. Where the deletion was smaller, some babies have apparently fed well and even breastfed and one child is described with an 'immense appetite'. However, most babies have fed slowly, been unable to cope with breastfeeding but managed better with a bottle. All babies with a larger deletion are described as having feeding difficulties but with persistence these have resolved, generally without the need for long term tube feeding. Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food passage, may occur.

All babies known to *Unique* have made slow but steady progress with feeding, eventually learning to drink through a teat or a spouted cup. Progress to solids has also been delayed and children have spent longer than usual taking pureed or mashed foods before learning to tolerate lumps.

> " He was unable to suck at birth and we never tried to breastfeed but for 15 days he was 'forcefed'. After that, feeding was slow but successful " - *15q22.1q22.3 deletion*

Growth

Where 15q15 is involved in the deletion, some children have had the tall, thin body build seen in children with Marfan syndrome. This is inconsistent, however, and at least one child with this larger deletion was thin but short.

Among children with a deletion of 15q21q22, the typical growth pattern appears to be initial growth delay so the child is short for their age; there is then rapid weight gain even in babyhood) around the abdomen so that the child is relatively plump for their height. This pattern of relative plumpness (truncal obesity) has been seen in adults, even when they have shown catch-up growth and achieved a normal adult height. The rapid weight gain is not always matched by a growth in height and at least two *Unique* members are described as extremely short for their age (as tall as a 3-year-old at nine years old); a 10-year-old is taking growth hormone to boost his height.

Medical concerns

Scoliosis

Half the children in this group developed a spinal curvature that at least needed monitoring. While the scoliosis was mild in some cases, in others it was severe and at least one child needed physiotherapy, a body brace and plaster casting to correct the developing curvature.

Craniosynostosis

In three children parts of the initially separate bony plates of the skull have fused together too early, causing the head to take on a very odd shape. In one baby, the soft spot (anterior fontanelle) on top of the head was already fused by the time the baby was born although a soft spot further back on the head was still open. When this occurs, the pressure inside the brain can be assessed to ensure that the usual shape of the skull is not putting undue pressure on the developing brain. Treatment may involve wearing a 'moulding' helmet or, if necessary, the plates of the skull can be released surgically. In one child with a 15q15.2q21.2 deletion, a large, covered defect in the scalp was found.

Brain

A baby with a very small or unusual-shaped head is likely to have imaging to check that the structure of the brain and pressure exerted by the unusual head shape are normal. In this group, three babies have been found to have an unusual brain structure. In one baby, the fluid-filled ventricles within the brain were somewhat larger than expected, in another the band of nerve fibres that links the right and left sides of the brain was underdeveloped; and in a third there was some sign of underdevelopment of the left side of the brain. Interpreting findings such as these is the job of a paediatrician or paediatric neurologist.

Heart

A child with a chromosome disorder can expect to have a careful cardiac examination, in particular in babies with suspected Marfan syndrome because of the known link between this syndrome and weakening of the walls of certain blood vessels and valves within the heart. Although one child with signs of Marfan syndrome has a leaky mitral valve (between the lower and upper chambers of the left side of the heart), this has not needed treatment or caused any particular problems by the age of 16.
Other heart conditions found in this group have occurred in babies with a larger 15q15q21/2 deletion. They have included holes between the upper and lower chambers of the heart and a variant of a complex heart condition known as tetralogy of Fallot, in which the circulation to the lungs is reduced. Tetralogy of Fallot needs to be corrected surgically.

Seizures

Three babies have developed seizures but these have been well controlled with medication.

Genitals

Fairly minor genital anomalies are quite common in children with a chromosome disorder and were found in half the boys in this group. The most common findings are undescended testicles at birth and treatment is usually a combination of watchful waiting with surgery to bring the testicles down if necessary. The genitals may be very small and occasionally the hole usually at the end of the penis is found on the underside instead (hypospadias); this is usually corrected surgically.

Pneumonias

Babies in this group were generally very vulnerable to respiratory infections in their first years but had generally outgrown this tendency by the age of nine or ten.

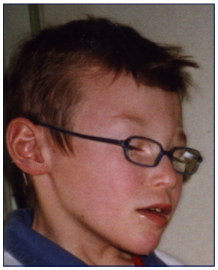
Outlook

The outlook for any child is determined largely by their clinical problems rather than their genetic karyotype. A significant number of babies in this group spent many weeks or months of their first year of life in hospital, but generally their health later improved significantly.

“ An extremely healthy boy **”** - *age 5*

Eyesight

Most children in this group old enough for an eye test were found to have a vision defect that needed correcting. The defects were quite varied but the most common was a degree of short sight. A child and an adult were found to have strabismus (squint), which can sometimes be corrected if necessary with glasses or surgery to re-align the eyes.



Hearing

From the information held by *Unique*, children with this deletion are no more likely to have a hearing impairment than other typically developing children.

Teeth

Dental disorders are seen more often among children with a chromosome disorder than among typically developing children. From the information held by *Unique* it seems that in this group, the top front teeth may be (or may appear) unusually broad and the teeth may emerge with wide gaps which eventually fill in. One child of 10 has missing teeth, including the canines.

Sitting, moving: gross motor skills

Babies and children with an interstitial deletion 15(q15q21) deletion typically appear to face delay in reaching their mobility milestones but the extent of the delay and the amount of support children need to acquire mobility is very varied. In some babies, mobility delay does not become apparent until towards the end of the first year.

In general, babies have learned to roll between seven months and four years and to sit between eight months and five years. Individual children have crawled between 10 months and two years and walked between 18 months and the latter half of the third year. Some children have gone on to climb stairs and run but this has not been possible for all, just as the ranges of achievement may not be possible for an individual child. Some youngsters have remained largely wheelchair-dependent, especially outdoors. General loose joints mean that children have often needed supportive footwear or splints especially for the ankles in the early stages of walking.

Using their hands: fine motor and coordination skills

Hand and eye coordination skills such as holding a bottle and playing with small toys may not develop in line with gross motor skills. Overall, there appears to be fairly consistent delay in hand use and fine motor skills as there is in toilet training but the degree of delay is very varied. The delay means that early intervention by occupational therapy to stimulate hand use is usually very helpful.

A five-year-old can wash his own hands and help with undressing and dressing but needs help with brushing teeth and bathing; he has difficulty with holding implements for writing. A nine-year-old finds it difficult to carry a plate; he recently learned to dress himself. At 16, one child can neither manipulate pencils nor cutlery and is totally dependent on adults for all aspects of her personal care. No child in this group is entirely toilet trained, but those with milder developmental difficulties appear to be day-time trained during the primary school years.

Speech and communication

While some delay in the emergence of speech and language is to be expected, the extent of the delay varies but tends to be marked and probably reflects the level of cognitive ability. Information, available on only six children, suggests that while some children acquire some speech, this may not be possible for all. Articulation is difficult for individual children and most are helped to communicate by using alternative means – eye pointing, touch, body language, pictures, sounds and signing in single words and linked phrases. Where speech has emerged, it appears to have done so in early childhood but has tended to stay at the level of single words and two-word phrases.

Learning

A child with an interstitial 15q deletion can be expected to have some learning difficulties or disabilities but it is not possible to predict the level of difficulty from the diagnosis or the karyotype. The range suggested by the medical literature and *Unique*'s membership is between moderate and profound.

Among youngsters with a moderate learning disability, individuals have shown particular skills with memory, in one case particularly visual memory.
All children can access a computer at least by switch and some children have acquired some independent drawing, writing and reading skills. Children with a moderate learning disability may learn to read and write using a limited vocabulary.
Placement in regular (mainstream) or special school varies depending as much on local provision as on a child's abilities and all children have needed a considerable level of support with their learning.

Generally sociable and affectionate

Behaviour

The evidence from *Unique* is that children are generally sociable and affectionate and families find very great reward in their child being able to communicate his feelings towards them. As babies there seems to be a tendency to be passive and inert but by the pre-school years a more positive aspect generally emerges. An 18-year-old was described as pleasant but with problems of emotional immaturity. Children usually do not understand safety constraints and need full-time supervision. As children understand their limitations more, frustration can develop and families describe episodes of temper tantrums and stubborn behaviour. Families who have tried methylphenidate have reported success. No particular pattern of sleep disturbance has emerged.

" A great sense of humour. He loves to tease " - *5 years*

" He likes to interact with people of all ages, music and sing-a-longs. Recently he has started to gives hugs and kisses and show affection and sadness, which we find very pleasing " - *9 years*

" He enjoys music, puzzles, computer games and activities that need visual competence. When he wins, he is proud! " - *10 years*

Puberty

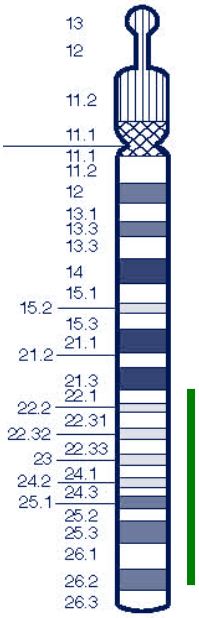
The little evidence available suggests that puberty usually proceeds normally. However, in one 14-year-old girl, no signs of puberty were to be seen.

Unique publishes a separate guide to the 15q24 microdeletion syndrome

Distal interstitial deletions between 15q22 and 15q26

When this information was compiled, *Unique* had one member family with a deletion in this area. This information is therefore derived chiefly from the medical literature. A difficulty with this approach is that in general it leads to babies and children with more serious problems being described, while those with less obvious difficulties may escape medical interest. There is also less information available on the development of these children.

One child has been identified with a microdeletion (so small that a conventional chromosome test appeared normal) at 15q24.1q24.2. This child had a mild learning disability, feeding difficulties, growth delay and a small head (de Vries 2005).



The information is drawn from the following: Dash 2006; Spruijt 2004; Schlembach 2001; Bettelheim 1998; Verma 1996; Formiga 1988; Kristoffersson 1987; Clark 1984; *Unique*.

The green line shows the rough area where the deletion has occurred. Pages with green bars by the page number are about deletions between 15q22 & 15q26.

At birth

In a number of cases, babies have had a difficult delivery, been delivered by Caesarean section after developing fetal distress and needed ventilation and intensive care directly after birth. However, where no diaphragmatic hernia or other major organ defect has been identified, some babies have experienced a much more normal delivery and immediate postnatal period and their chromosome disorder has only been discovered after feeding difficulties and developmental delay emerged.

Development

All children have shown a degree of developmental delay, but there is some uncertainty over the severity. While some children with a deletion between 15q24 and 15q26 seem to have shown a marked delay, in at least two children the degree of delay was probably only moderate. One child, walking normally at 20 months despite mildly low muscletone, was assessed as having a moderate learning difficulty. Another child, with a developmental age of a 19-month-old at the age of 3 years and particular delays in expressive language and hand use and coordination (fine motor skills) was described as cheerful and strong-willed, if easily frustrated. A 14-year-old with a deletion between 15q23 and 24.1 was sitting independently at 11 months and walking alone by 16 months. He had severe learning difficulties but used speech as his main means of communication. He also had difficulties in using both hands simultaneously to handle cutlery.

Growth

Babies typically grow slowly in the womb and are small-for-dates at birth. The slow growth rate has been noticed as early as 16 weeks into the pregnancy. At birth at or near term, babies have weighed between 2.95kg (6lb 8oz) and 1.46kg (3lb 4oz). Babies' small size is generally proportionate, that is, their weight is what you would expect for their length.

In one case, a baby with a deletion between 15q21 and 15q24, growth in the first year of life was normal, despite somewhat small size at birth. A young boy with a 15q23q24.1 deletion was average height until he entered his growth spurt at puberty, when he became tall and slim.

Appearance

Among the facial similarities between babies and children, a number of babies with a deletion encompassing 15q25 have been noted to have fine, fair hair and blue or pale eyes. Other unusual features noted have included a bulge down the middle of the forehead, narrow or almond-shaped, upslanting and sometimes widely spaced eyes, large or prominent ears sometimes set low on the side of the head or with a curly top, a small nose with thick nostrils, a small mouth with thin lips and a receding chin.

Growing up with a 15q23q24.1 deletion. Left: age 2½ years; above: age 14 years

Hands and feet

Most babies are born with slight anomalies of their hands or feet. These do not usually affect the way they use their hands, but one child needed surgery to correct his 'finger-like' thumbs. Abnormal foot positioning may affect walking and correction can be helpful. Anomalies include a single palm crease on the hands, incurving fifth fingers, short hands, puffy hands and feet, unusually positioned toes and talipes equinovarus (club foot), where the foot is positioned pointing inwards and downwards. One boy had 'clawed' big toes that caused balance problems.

Medical concerns

Diaphragmatic hernia

In babies with a deletion of 15q24q26 and perhaps specifically loss of the *NR2F2 (COUP-TFII)* gene at 15q26, the diaphragm that separates the contents of the abdomen from those of the chest cavity may not develop properly. When this occurs, the contents of the stomach may protrude into the chest cavity, not allowing the lungs enough room to develop properly. There are various degrees and types of this condition, known as a diaphragmatic hernia (see p11) and depending on the type and severity, it may be detectable on mid-trimester ultrasound scans or not be detected until after birth. A baby born with a large diaphragmatic hernia will usually need respiratory support or ventilation at birth and surgical repair of the hernia in order to allow the lungs space to develop. In the past, outcomes from this surgery have not always been very successful, but techniques and outcomes continue to improve. Repair of small or partial hernias is generally more straightforward.

Kidneys

Anomalies of the kidneys have been found in 7/11 babies. Treatment will depend on the nature of the disorder and in some cases only monitoring may be needed.

Heart

Anomalies of the heart have been found in five babies out of 11, but in at least one the narrowing of the vessel that takes blood from the heart to the lungs was not sufficiently severe to need surgical repair.

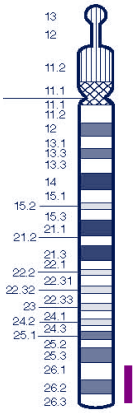
Eyesight

One research group has recently reported the possibility that a gene linked with keratoconus is to be found at 15q22.32q24.2. Keratoconus is a degenerative condition where the cornea thins and is pushed outwards, usually in the centre, by the internal pressure of the eye. If untreated, it can result in a rupture, but sometimes it may stop in an earlier stage of if its development or simply not progress that far. It is a condition which requires to be regularly monitored. In mild cases, spectacles will offer correction of the refractive problems. Contact lenses may be required for more advanced cases. It is not yet known for certain whether children who have lost this gene will be at risk for development of keratoconus (Dash 2006).

Outlook

With so few babies and children described, we cannot be certain about outcomes. Conditions such as a diaphragmatic hernia or significant heart condition are as important in considering a child's future as their chromosome make-up. The outlook does look better for babies without significant organ defects at birth.

Unique publishes a separate guide to 15q26 deletions



Deletions from 15q26

Some sixteen cases with a pure deletion in this area are described, at least nine in the medical literature and seven members of *Unique*. The oldest member of *Unique* was nine years old when this leaflet was written and the oldest person described in the medical literature was 13 years old (Davidsson 2008; Klaassens 2005; Kuechler 2005; Pinson 2005; Biggio 2004; Okubo 2003; Tonnies 2001; Rogan 1996; Siebler 1995; Roback 1991; Pasquali 1973; *Unique*).

The purple line shows roughly where the deletion has occurred. Pages with purple bars by the page number are about deletions from 15q26.

Pregnancy and birth

In the cases where pregnancy was described, the size and growth of the baby virtually always gave grounds for concern. The baby's small size was noted by mothers from 25 weeks into the pregnancy but may well have been evident even earlier. In other ways, most mothers reported a normal pregnancy, although in two cases there was very little amniotic fluid around the baby (oligohydramnios). A late pregnancy anomaly scan suggested a possible heart defect in one baby.

Due to the baby's small size, most mothers have found that their pregnancy was treated as 'high-risk', with frequent monitoring and usually specialist hospital care.

At birth

Babies have generally been closely monitored in the second half of pregnancy and concern for their wellbeing has meant that some babies were delivered a few weeks early by Caesarean section. Among babies born at or near their due date, birth weights were all low, ranging from 1.263kg (2lb 13oz) to 2.664kg (5lb 14oz). Babies were generally small overall, with their head in proportion to the rest of their body. Apgar scores (the 0-10 scale of a baby's wellbeing at birth) were typically low but showed an improvement after five minutes. Many babies needed support with their breathing in the first hours and some needed care for some weeks after birth, partly because of their small size and feeding difficulties and partly due to their medical problems.

Appearance

Apart from babies' small size, there is usually little sign of an underlying disorder. You or the doctors may notice some unusual facial features. These may mean that a baby looks more like other babies with a 15q26 deletion than like his own family

Some of the most common features seen include a relatively small chin and lower jaw that may be set back against the upper jaw; a triangular face, wide set eyes with small openings and low set ears that may be large and may be tilted backwards.

Hands and feet

Minor anomalies of the hands and feet are relatively common in children with chromosome disorders. These may just be cosmetic or they may make it harder for the child to use their hands or to walk. The most common features affecting the hands are cosmetic and include incurving fifth fingers sometimes with a single crease, small, puffy hands, tapering fingers and an unusual placement of the thumbs.

Children's feet are typically small and may be so small that weight-bearing and walking is difficult. In some cases the feet are very flat or they may have a curved sole, like a rocker on a chair. A few children are born with one or both feet turned in and two children were born with club feet that needed surgical correction.

Feeding

The evidence from *Unique* is that babies have needed considerable support to establish effective feeding. At first they may show no interest in feeding, be unable to suck effectively or to coordinate the actions of sucking with swallowing. Most babies have needed long-term support and were fed either through a nasogastric tube or a gastrostomy tube direct into the stomach for weeks or even longer. Some babies have succeeded in bottle feeding.

Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food pipe, affected some babies. Reflux raises a baby's risk of inhaling food contents and setting up an infection in the lungs known as aspiration pneumonia. Reflux can be eased by careful semi-upright positioning during and after feeds, sleeping in a prescribed sleep chair rather than a bed, raising the head end of the baby's cot and if necessary by prescribed medication that helps to keep the feed within the stomach and counteract any acidity. Babies who have continuing problems can have a surgical procedure called a fundoplication to improve the action of the valve at the junction of the food pipe and stomach. Where feeding and reflux problems are persistent, a gastrostomy tube (PEG, button) can be inserted to allow direct feeding into the stomach until the baby is sufficiently mature to tolerate feeding by mouth.

All babies known to *Unique* have made slow but steady progress with feeding, eventually learning to drink through a teat or a spouted cup. Progress to solids has also been delayed and children have spent months or even years taking pureed or mashed foods before learning to tolerate lumps. Lack of appetite appears to be persistent and enriched milks are usually needed, with some children still relying on a gastrostomy tube as toddlers and at school for all or some of their feeds. Some children have needed therapy to increase their oral tolerance, with generally good results.

> " She will still really only drink water or liquid by force. She is fed orally three times a day but is a very reluctant eater and is tube-fed water and milk overnight " - *age 3*

> " Unable to breast or bottle feed due to swallowing difficulties; NG tube fed for the first two years. Then she learned to drink and can now eat purees but is also gastrostomy fed for 10 hours a night " - *age 5*

> " She is still very orally defensive. She is fed predominantly by G-tube but has progressed to taking yogurt by mouth and small bits of cracker. She now allows me to brush her teeth too - a huge step! " - *age 7*

Growth

All children known to *Unique* or described in the medical literature were born small for dates, although the degree of growth delay varies, with some babies born more than twice as heavy as others. At birth, the evidence is that babies are small overall – their length, weight and head circumference are all low and generally in proportion.

Growth in length/ height after birth is also very slow and most families will be referred to a child growth specialist for an opinion on likely adult height and treatment with growth hormone.

There is evidence that some children with a 15q26 deletion are at risk of gaining too much weight relative to their height and becoming fat around the abdomen. In some cases, this may be due at least in part to overfeeding and it is important that both height and weight are monitored but also the ratio of weight to height.

Age 4, with 2-year-old brother

Underlying the very slow growth is the loss from the 15q26.3 band of the *IGF1R* gene (insulin-like growth factor 1 receptor gene), a gene that is involved in growth regulation. A normal growth pattern is determined by a complex of factors, including the processing by the body of chemicals known as growth factors. Children who have lost the *IGF1R* gene are resistant to one of these growth factors, known as insulin-like growth factor 1. As a result, levels of IGF1 may be very high, but the body is unable to make use of them.

> “ At the age of 13, he was as tall as an eight-year-old ”

> “ At first, she was prescribed the regular amount of formula for babies and became very chubby. The geneticist recommended we cut back to thin her out and make it easier for her to move. We learned to gauge how much she needs and she looks much healthier. Although very small for her age, she is perfectly proportioned ”

Medical concerns

Heart

Defects in the structure of the heart are seen quite commonly in babies with a chromosome disorder. Ten of the 17 babies with a 15q26 deletion were affected, and while some of the heart conditions consisted of holes between the upper or lower chambers of the heart (atrial septal defects/ASD; ventricular septal defects/ VSD) or between both chambers, other babies had more complex cardiac conditions. From *Unique*'s experience, most babies have needed corrective surgery but have done well afterwards, including a baby born with hypoplastic left heart syndrome, where the left side of the heart has not developed properly and is very small and the aorta, the artery that takes blood from the heart around the body, is tiny and blood can only reach it through the ductus arteriosus, a blood vessel that normally closes within days of birth. In the early years, babies with a complex heart condition or one that has not yet been fully corrected may need supplemental oxygen.

A number of genes near the end of 15q are believed to be implicated in heart development, including one called *NF2R2* at 15q26.2, a gene that may be essential for proper development of the blood vessels and heart, and another known as *MEF2A*. The *IGF1R* gene that underlies growth problems is probably also an important player in heart development (Davidsson 2008).

Diaphragmatic hernia (see page 12)

Quite a few babies with a deletion of 15q26 (possibly as many as half) have been born with a defect known as diaphragmatic hernia in the muscular wall that separates the contents of the chest, in particular the lungs, from the contents of the abdomen. As part of the bowel, stomach or liver take up space in the chest, potentially depriving the lungs and heart of room to develop properly, this is a serious condition that needs surgical correction soon after birth. One study of babies with a diaphragmatic hernia and a 15q26 deletion has shown that all the children were missing a small region at 15q26.1q26.2 and so it is believed that a gene or genes that are essential for the normal development of the diaphragm must be found there, quite possibly the gene called *NR2F2*.

Kidneys

A baby with a 15q26 deletion will probably have a careful check of the kidneys because this deletion appears to affect the development of the kidneys in possibly half of all babies. One kidney may be found in an unusual position (ectopic) but be working normally, or one or both kidneys may be unusually small and have reduced function.

Defects of the lower spine

Three children in this group had a defect in the formation of the lower spine. One baby had a sacral dimple (a small pit or hole). 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 any underlying problem. All the same, matter 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 or the colon. Another child

had incomplete development of the vertebrae, the bones that form around the spinal cord, and in another, imaging of the mid to lower back because of a birthmark revealed a tethered cord. In this condition, the bottom end of the spinal cord that usually floats freely in a pool of spinal fluid is attached instead. As the child grows and moves, this causes the spinal cord to stretch, leading to symptoms such as muscle weakness, loss of sensation and difficulties with bowel and bladder control.

Outlook

The outlook for any child is determined largely by their clinical problems rather than their genetic karyotype. Babies born with a diaphragmatic hernia and babies with a heart condition are likely to need more medical care in their early years than typically developing babies. As a group, children with chromosome disorders are more liable to develop respiratory infections than other children and tend to be more unwell when they catch them. In time, like typically developing children, they outgrow this tendency and *Unique* families report that by school age or by the age of 8 or 9, their children are generally healthy.

Eyesight

The most common eye problem, seen in four children, was a squint (strabismus). This may affect one eye or both and the direction may be inward or outward. Severity also varies, with the condition resolving naturally in some babies, requiring monitoring and surgical correction in others. In one child hand use was delayed until her short sight was corrected.

Hearing

Young children are vulnerable to the fluctuating, temporary hearing loss caused by a build-up of fluid within the middle ear behind the ear drum. This was found in three young children with a 15q26 deletion and successfully treated by inserting aeration tubes into the eardrums. No children were found to have a permanent hearing loss.

Teeth

Dental disorders are seen more often among children with a chromosome disorder than among typically developing children but only two children with a 15q26 deletion are known to be affected. In one, the back teeth emerged before the front teeth; in the other, the teeth were very slow to erupt and one upper molar tooth was missing.

Sitting, moving: gross motor skills

Babies and children with a 15q26 deletion typically appear to face delay in reaching their mobility milestones but the extent of the delay is varied. Part of the difference between individual babies is due to underlying health problems, such as heart conditions, and part also due to features such as very small feet or feet that need surgical correction before walking becomes possible. Babies tend to have low muscletone but with maturity and physiotherapy, this generally improves so that some children outgrow their hypotonia. Joints are typically hypermobile and children may need support in the form of splints, supporting boots, standers or walkers, to become mobile. In one child the head of the radius (the outer, short bone in the forearm) dislocated spontaneously at the age of seven but surgery was not needed.

Babies in this group learned to roll over between the ages of six months and two years and were able to sit up between 14 and 30 months. Those babies who crawled started between eight months and three years, while others scooted or bottom-shuffled, mostly starting in their third or fourth years. While one girl learned to walk within two months of her club feet being corrected shortly before her third birthday, and others were walking by three or four, at least one child is not yet walking at the age of seven.

“ She propels herself in a manual wheelchair. She is very good at manipulating the chair, but prefers not to stop. She likes to go down ramps and go fast! ” - *age 7*

Using their hands: fine motor and coordination skills

Information from *Unique* shows that hand and eye coordination skills such as holding a bottle and playing with small toys may not develop in line with gross motor skills. Overall, there appears to be fairly consistent delay in hand use and fine motor skills as there is in toilet training. This delay means that early intervention by occupational therapy to stimulate hand use is usually very helpful. Individual children have particular problems: one girl found it hard to hold her hands with the palms upwards and preferred to push with her thumbs than her fingers.

Toilet training comes late, with control emerging in individual children by the age of seven. Children will learn the personal care skills of helping to dress and undress, but some may never become totally independent.

Speech and communication

While some delay in the emergence of speech and language is to be expected, the extent of the delay varies and probably reflects the level of cognitive ability. Information, available on only seven children, shows that they typically use a mixture of sign language and speech, as well as vocalizing, gesture and expression to communicate their needs. Two babies had a very soft cry. Where children do use words, these have generally first emerged between the ages of two and five. Most children have some difficulty in making the sounds of speech clearly enough to be well understood by people outside family and school. Speech therapy is generally described as ‘successful’ or ‘excellent’. One child with a moderate speech delay showed catch-up with her typically developing peers by the age of 10 years.

The snapshots below indicate the range of speech and language in individual children.

“ She definitely understands situations, though not 100 per cent sure of understanding of instructions. She can express herself well ” - *age 3*

“ She first communicated with tongue clicks and raspberry noises; then learned to sign and then speak at 4½ years. Today, she uses simple sentences. Her understanding is ahead of her speech but the gap is narrowing as her speech is improving rapidly. She is softly spoken and has to concentrate to get the sounds out ” - *age 5*

“ She speaks in full sentences but often forgets words and names ” - *age 5*

“ She has a vocabulary of over 100 words in sign language and 50 to 75 words of speech ” - *age 7*

Learning

A child with a 15q26 deletion can be expected to have some learning difficulties or disabilities but it is not possible to predict the level of difficulty from the diagnosis or the karyotype. Some children appear to have only a slight difficulty, attend a regular mainstream school and learn to read, write and compute with their typically developing peers with problems only over concentration and some fine manipulative skills. However, this is not possible for all and at least one child within *Unique* has a profound learning disability. Overall, the evidence suggests that most children do well in a mainstream school with a level of 1:1 support, at least for primary education, although this depends on local arrangements.

Some children have strengths in the field of music and may be able to sing or hum in tune even when they have no language; and some show great determination in learning new skills. Abilities like memory vary widely between individual children. At least one child has particular problems with visual or spatial relationships.

Behaviour

The evidence from *Unique* is that children are generally sociable and have a happy temperament. Their behaviour is in general good, although they may find their disabilities frustrating and express this by whining, shouting or being destructive. *Unique* has no reports of self harming behaviour. One child has been described as within the autistic spectrum.

“ She enjoys playing with other children, loves noisy toys, TV and music. Her behaviour is good unless she is very tired ” - *age 3*

“ A happy and very loving child; she is really brave taking all medical procedures in her stride; has a great sense of humour and makes us laugh a lot. A very active and sociable little girl who is keen to talk to everyone and can be inappropriately friendly to strangers. She enjoys emptying and filling things and this behaviour can be challenging, eg she will empty the fridge and pour the contents out all over the floor. She can also be rather destructive, likes to tear paper and throw objects ” - *age 5*

“ She tends to play with one toy for hours, pushing the same buttons over and over and needs directing towards other, more physical activities ” - *age 7*

Support and Information

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

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

This 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. It was compiled by Unique and reviewed by Dr Ute Moog, Clinical Genetics Department, University Hospital Maastricht, The Netherlands and by Unique's chief medical advisor Professor Maj Hulten BSc PhD MD FRCPath, Professor of Medical Genetics, University of Warwick, 2006.

2006 Version 1 (PM)

Rare Chromosome Disorder Support Group Charity Number 1110661
Registered in England and Wales Company Number 5460413