

Support and Information



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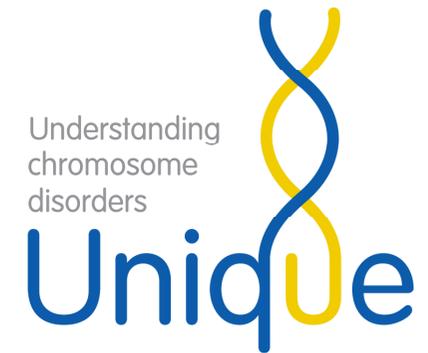
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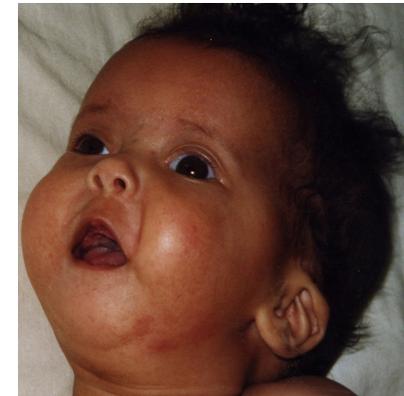
This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The guide was compiled by Unique and reviewed by Dr Kamilla Schlade-Bartusiak PhD, Department of Medical Genetics, University of Alberta, Canada and by Professor Maj Hultén BSc PhD MD FRCPATH, Professor of Reproductive Genetics, University of Warwick, UK 2007. (PM)

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14q deletions from 14q31 and 14q32.1

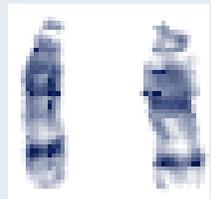


Sources and references

The information in this leaflet 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 original articles on the internet in PubMed. If you wish, you can obtain abstracts and articles from *Unique*.

The leaflet also draws on *Unique*'s database. When this leaflet was written, *Unique* had 54 members with a 14q deletion, of whom 29 had a pure 14q deletion with no other chromosome involved.



Two chromosome 14s, stained and magnified

14q deletions

A chromosome 14 deletion means that part of one of the body's chromosomes has been lost or deleted. If the material that has been deleted contains important instructions for the body, learning disability, developmental delay and health problems may occur. How obvious these problems are depends on how much of the chromosome has been deleted and where the deletion is.

Genes and chromosomes

Our bodies are made up of billions of cells. Most cells contain a complete set of genes. We have thousands of genes. Genes act like a set of instructions, controlling our growth and development and how our bodies work.

Genes are carried on microscopically small, thread-like structures called chromosomes. There are usually 46 chromosomes, 23 inherited from our mother and 23 inherited from our father, so we have two sets of 23 chromosomes in 'pairs'. The chromosomes and the genes are made up of a chemical substance called DNA.

Chromosomes come in different sizes and 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, generally from largest to smallest. Each chromosome has a short (p) and a long (q) arm.

In a 14q deletion, material has been lost from the long arm of one of the two chromosome 14s. The short arm of chromosome 14 contains no unique genes, so losing material from the short arm generally has no harmful effect.

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

Chromosome deletions

A small or a very large piece of the chromosome can be missing. If the piece is visibly missing when the chromosomes are magnified as much as 1250 times under a microscope, it is called a **deletion**. The missing piece may be so tiny that the magnified chromosome looks normal and it can only be found using recently more developed techniques, such as FISH or array-CGH. It is then called a **microdeletion**.

One type of deletion is called **terminal**. There is one breakpoint and the chromosome from the breakpoint to the end of the arm is missing. Another type of deletion is called **interstitial**.

There are two breakpoints on the same arm that have rejoined and the part of the chromosome between them is missing.

Terminal deletions from 14q31 and 14q32.1 are usually larger than interstitial deletions, so that more genes are missing.

"Each day is different – from angel to devil!" - 14 years

Personal care and independence

Self care skills are late to develop and children are typically late to be toilet trained, although the range of achievement is very broad. One child was toilet trained at two years; other teenagers are still not ready to begin training.

This broad range of ability, which also applies to feeding skills, means that it is not possible to predict from the chromosome deletion alone what level of independence any individual child will achieve. What is known is that there are adults with this chromosome deletion living happily in community settings with varying degrees of support and others who do not appear likely to achieve this level of independence.

Puberty

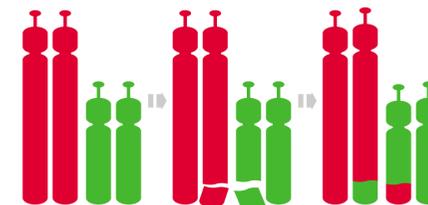
From the evidence available, puberty appears to have proceeded normally at the expected age.

"The most joyful kid I have ever seen."

E has a 14q deletion and additional material from the long arm of chromosome 9.

Two-year-old E can roll over by himself and push off with his legs when lying on his back. For indoor use, he has a special chair for feeding and playing at his table and a walking bike where he is fixed at the hips and chest and can move forwards and back as well as a wheelchair for outdoors.

E smiles and laughs a lot and cries from hunger or tiredness and his family interprets his needs. He is starting to anticipate: he cries if he sees a toothbrush and knows when it's time to sleep or play. Medically, E has had a few problems: he has an inefficient valve in his heart; his ear canals are very narrow and he has frequent ear infections so he has been to hospital frequently. He has had spells where he stopped breathing and his windpipe is narrow.



A balanced translocation

How did this happen?

Some 14q deletions are the result of a rearrangement in one parent's chromosomes. This is usually a **balanced translocation** in which material has changed places between chromosomes but no material has been lost or gained and the parent usually has no difficulties with health or development.

Other 14q deletions occur when both parents have normal chromosomes. The term that geneticists use for this is **de novo (dn)**. De novo 14q deletions are usually caused by a change that occurred when the parents' sperm or egg cells were formed.

We know that chromosomes must break and rejoin when egg and sperm cells are formed but this only occasionally leads to problems.

The breaking and rejoining is part of a natural process and as a parent you cannot

pictures but is not reading or writing yet” – age 14

■ Speech and communication

Children will typically experience a marked speech delay and speech and language development appears to reflect the level of learning disability. Most children appear to understand better than they can express themselves and benefit from communication aids such as talking boards used alongside or instead of speech. Individually, children are resourceful and communicate using gestures, vocal noises, pushing and pulling.

Where words have emerged, the age range for first words is extremely broad (nine months to 10 years). A child who was using single words at nine months was talking in sentences by four years. A child who first spoke at 14 months was speaking clearly in two languages at nine years, using 3 to 4 word phrases, but only using long and complex sentences ‘when she wanted to’.

Articulation may be unclear so that words are hard to make out and children benefit from consistent speech therapy.

■ Eyesight

The most common vision problem in this series is strabismus (squint), usually correctable with glasses or patching; however, children may not wish to wear glasses consistently. Other problems affecting eyesight have included a mild astigmatism (curvature of the cornea at the front of the eye), long and short sight and coloboma (a developmental defect of the eye). One child had retinal dystrophy (a disease of the light-sensitive layer at the back of the eye) and a problem with night vision. Another child had hooded eyelids (ptosis), but this did not affect vision.

■ Hearing

There is no evidence from this series of any child with a permanent hearing loss. Five children had repeated middle ear infections, resulting in the temporary hearing loss known as glue ear, that was relieved by the insertion of tubes into the eardrum, in most of the children repeatedly (up to four or five times) until they outgrew their vulnerability to ear infections.

Behaviour

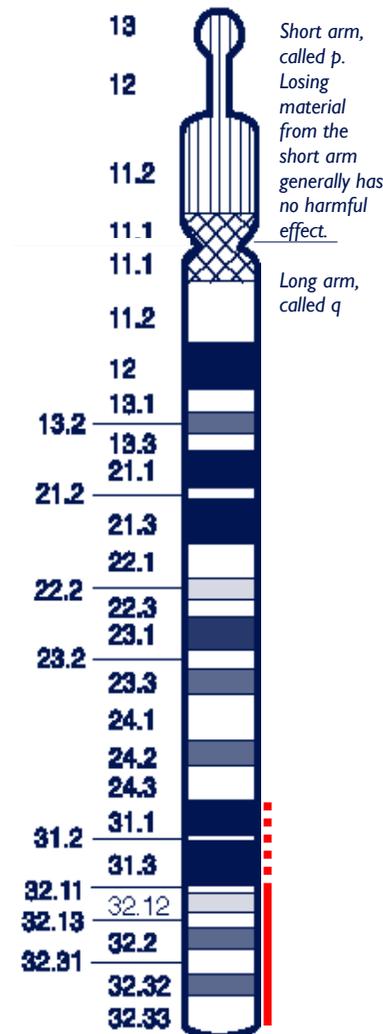
No specific behaviour disorders have been identified in people with this chromosome deletion and individuals are usually described as friendly, good-natured and loving. As young children, they may be late to mature into an ability to play with other children and need more 1:1 attention than other children but with maturity they learn to enjoy television, music and computers, like other children. Because of their physical limitations, as a group, these children are unlikely to take particular pleasure in outdoor or active pursuits.

One young adult developed challenging behaviour and autistic tendencies but responded well to treatment with medication. Another child with attention deficit hyperactivity disorder also responded well to medication.

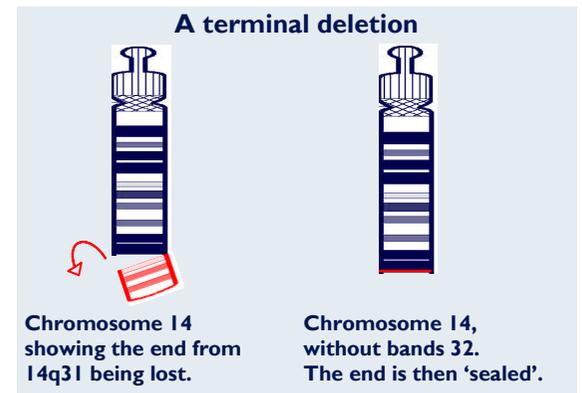
“Very gentle and sociable, lots of kisses and tells her Mummy she loves her all the time!” - 10 years

This leaflet tells you what we know about **interstitial and terminal deletions from bands 14q31 and 14q32.1**

Your geneticist or genetic counsellor can tell you more about the chromosome material that has been lost. You will almost certainly be given a **karyotype**, a shorthand code for the image of your child’s chromosome make-up that will show the points where the chromosome has broken and rejoined. Your child’s karyotype may look very like another person’s, from *Unique* or in the medical literature, or it may look exactly the same. But even in people with the same karyotype, the chromosome may have broken at a different point within the same band. This is one important reason why people with apparently similar karyotypes do not all have the same problems or features. Individual differences can be quite marked and it is very important not to make direct comparisons between your child and others. After all, each of us is unique.



Some seventeen cases with a pure deletion in this area of 14q are described. Eight have a terminal deletion, with a breakpoint between 14q31 and 14q32.1. At least five have been described in the medical literature and three more are members of *Unique*. Nine others have an interstitial deletion, removing part of bands 14q31 and 14q32. Of these, six have been described in the medical literature and *Unique* has three members. In addition, three members of *Unique* have a terminal deletion of 14q as well as loss or gain of material from another chromosome (chromosomes 9, 17 and 21) (Mertens 2000; Spruijt 2000; Byth 1995/3, 4, 5; Lurie 1994; Bonthron 1993; Gorski 1990; Masada 1989; Yen 1988; Nielsen 1978; *Unique*).



Of six cases where the **pregnancy** was described, it was quite normal in four. In two pregnancies where difficulties arose, the deletion was terminal. In one, the baby's growth tailed off at five months, there was placental separation, the level of amniotic fluid was very low (oligohydramnios) and the baby was born two months early; in the other, affected by severe polyhydramnios (excess amniotic fluid), the baby, in whom enlarged ventricles (the fluid-filled spaces within the brain) and other anomalies had been seen on ultrasound scan, did not survive delivery at 37 weeks.

At birth

What was unusual	How many babies affected?
■ Premature birth	3/17
■ Respiratory distress at birth	2/17
■ Feeding difficulties	5/6
■ Unusual facial features	15/15

Range of birth weights at term: 4.4kg (9lb 11oz) to 2.25kg (4lb 15oz)

■ Premature birth, respiratory distress

Most babies were born at or near term, with three babies born prematurely at 31 to 37 weeks. One baby, born at 31 weeks, an appropriate size and weight for gestation, was in good condition at birth and grew up healthy. Another baby stopped growing five months into the pregnancy and was born at 32 weeks (see *above*). A third baby with a mosaic constitution (cells with a normal chromosome make-up and cells with the deletion) was born at 37 weeks (see *above*) (Mertens 2000; Spruijt 2000; *Unique*).

From the slim evidence available, it appears that Apgar scores (measures of general wellbeing at birth, on a scale 0-10) may be low and at least one baby with oesophageal atresia (narrowing of the food passage) and a tracheo-oesophageal fistula (abnormal channel linking the windpipe with the food passage) had respiratory distress at birth. Birth weights at term were also generally low, and there was no obvious difference between babies with an interstitial and a terminal deletion. The mean weight of 3.1kg (6lb 13oz) shows that most babies were small at birth.

■ Feeding

Apart from unusual floppiness (hypotonia), the most frequent observation at birth was feeding reluctance, with mothers not able to breastfeed. Babies typically sucked too weakly to meet their own nutritional needs and some had problems with swallowing, the size of the oesophagus (very narrow) or with the movement of feeds through the oesophagus. The evidence suggests that most babies will need careful feeding in the early days to ensure steady growth and weight gain.

Although not seen commonly, gastro oesophageal reflux (GERD, GORD, where the stomach contents flush readily back up the food passage) may also occur and cause two secondary problems, an inflammation of the food passage (oesophagitis) and aspiration, where the returned feed is inhaled into the lungs, with the risk of causing an infection.

was mild, one child wore a corrective brace and was awaiting surgery to straighten the spine.

Five people also had abnormally mobile joints, usually requiring support or splinting.

Among children with delay in gross motor skills, rolling over was achieved between seven and 12 months; sitting between eight and 18 months; cruising or crawling between 22 months and eight years and walking between 11 months and nine years.

A thirteen-year-old who walked at nine years does not run but can walk fast and can climb stairs holding on to railings. At 13, she was still working on getting to a standing position from sitting. A fourteen-year-old who walked at 7 years was climbing stairs within months and could run by 12 years. For longer distances, she still relies on a stroller.

By contrast, a girl with a small deletion within 14q31 was riding a bicycle and able to swim short distances independently by the age of six and swimming long distances alone at nine years.

■ Using their hands: fine motor and coordination skills

There is little specific evidence on this group of children, but babies are typically late to reach out and grasp for toys, to hold a bottle or toys and to transfer toys from one hand to the other. They spend longer than other babies feeling and handling clothes, objects, faces and hands and benefit from stimulation and early access to occupational therapy. The pace of development is individual, but a thirteen-year-old was reaching for objects and making choices; able to pick up a spoon but still dropping it when it got to her mouth. She could hold her own drink bottle and applied extra stimulation by tapping her thumbs together as she drank. By contrast, a nine-year-old was able to dress herself although she had difficulties with fastenings, and to feed herself well with a spoon and fork, but had greater difficulties with a knife. She could brush her own teeth if reminded.

■ Learning

A degree of learning disability is typical, but the extent is variable and may be slight. From the very small body of evidence available, it seems that a mild to severe disability (IQ range 35-84) can be expected and that some youngsters may face greater difficulties with age. In one family with a three-generation deletion within band 14q31, the grandfather worked successfully as a tradesman, the mother completed elementary school and the child had borderline learning difficulties. Some older individuals have learned to read and write and there is some evidence that memory can be excellent in specific areas (Byth 1995; *Unique*).

“ Prefers the keyboard to books or paper. She has a very good memory and can explain and retell Disney films well. She recognises common short words; she attends a special school ” – age 9

“ Very determined, she never gives up, but does things when she wants to. She has no verbal, drawing, writing or reading skills yet. At present, being home schooled because the school was not supplying 1:1 and she was in a classroom with children with behaviour problems and sustained four concussions ” – age 13

“ Currently achieving at a 2-6 year level, higher in some areas. She started to use a keyboard at 7 and has a very good memory when she wants. She looks at books with

How many affected children?

■ Growth delay	At least 4/11
■ Proportionately small head	3/7
■ Developmental delay	Most
■ Low muscle tone (hypotonia)	At least 7/11
■ Learning difficulties	Most
■ Eyesight problems	6/15
■ Hearing problems	6/15

■ Growth

Most babies with a deletion from near the end of 14q appear to grow slowly after birth, with their growth curve typically at or below the lowest line on a growth chart.

The evidence suggests that stature is proportionately small, affecting height, weight and head circumference. In this situation, additional feeding may boost weight without any effect on height. At least one child has been treated with growth hormone but it is too early to be certain what the long-term outcome of this treatment will be.

However, not all people with a deletion from near the end of 14q are short: two adults have been described with a normal height and weight.



■ Head and brain

Measurement of the head circumference shows a varied picture, with some babies' heads being unusually small (within or near the lowest three per cent of the population). Scans of the brain have usually shown a normal structure, although one baby had

agenesis of the corpus callosum (ACC), the absence of the band of nerve fibres that normally links the two hemispheres of the brain. Another baby had a maldevelopment of part of this band of nerve fibres.

■ Sitting, moving: gross motor skills

Most babies and children with a deletion from near the end of 14q do face some delay in reaching their mobility milestones, but the picture is quite varied. Children with a small deletion within band 14q31 and one child with a 14q31.1 terminal deletion reached their mobility milestones within the normal time;

among the others, the range of achievement was very broad and some children were very late to start walking although all did so eventually.

Behind the delay is a considerable degree of hypotonia (low muscle tone) and muscle weakness, which usually improves with maturity and practice (physiotherapy), although it was still slightly evident in a man of 27 years. In one child there was asymmetrical distribution of tone. Six children had a diagnosis of spinal curvature, either a sideways curve (scoliosis) or a forwards curve (kyphosis). While in some children, the curvature

Reflux can be eased by careful semi-upright positioning during and after feeds, raising the head end of the baby's cot, giving thickened feeds and if necessary by prescribed medication that helps to keep the feed within the stomach. 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 passage and stomach.

Feeding difficulties proved to be persistent in at least three children, with soft textures needed and a resistance to lumpy or chewy foods into the teen years. One child showed multiple food intolerance until adolescence.

Children with a chromosome disorder are prone to develop constipation, due in part to their relative lack of mobility and activity, in part to their necessarily high-energy, low-fibre diet and in part to a relatively low fluid intake. If it is not possible to adapt the diet – and it may well not be – then early treatment with laxatives should prevent the problem from becoming acute.

Additionally, one child has an allergy to dairy products, raw egg and certain medications including penicillin but this is not considered to be associated with the chromosome deletion.

“ She was labelled 'lack of will to thrive' ” – 14q32qter deletion

■ Appearance

There may be little sign in the appearance of a newborn baby of the underlying disorder. Doctors may notice what are known as 'dysmorphic features' which may or may not be obvious to a parent. These features can mean that a baby or child with this chromosome disorder looks more like others with the same disorder than like members of his or her own family.

Typical features can include: an asymmetrical face with full cheeks, a prominent forehead, bushy eyebrows, wide set eyes with tiny skinfolds across the inner corner (epicanthic folds), low, prominent or cupped ears, an upturned nose with a broad, low bridge, a thin upper lip, a small chin and jaw, a short neck and fine, sparse hair. The palate is typically high arched and the uvula (the flap of tissue hanging from the back of the soft palate at the back of the mouth) may be split or unusually placed. One baby had thickened gums; another had a deep midline crease in the tongue and a divided tip. One child had crowded teeth, two others had small or abnormally formed front teeth in either the upper or lower jaw.

■ Hands and feet

Minor, non-functional anomalies of the hands are relatively common in children with chromosome disorders. In this group, a wide variety of unusual features was seen, including clenched fingers, a single palm crease, short thin nails, long fine fingers and toes, an additional joint in the thumbs or odd placement of the thumbs, and short, chubby hands and fingers with a chunky appearance.

Foot problems are more likely to need correction before or once a child starts walking and in this group included in- or out-turned feet, the slight incurving known as banana foot (metatarsus adductus), a clawed appearance due to bent big toes, a large 'sandal gap' between the first and second toes, and overlapping toes. Three children are described with extremely flat feet, and in one case even surgery did not correct them.

Medical concerns

	How many children affected?
■ Seizures	6/15
■ Minor genital anomalies	6/7 boys; 0 girls
■ Heart condition at birth	2/15
■ Abnormalities of temperature control	2/15

■ Seizures

Six of the 15 children in this group have experienced at least one seizure, although they have had many different types of epileptic activity. One baby experienced clonic jerks (repeated jerking) at five days; these were controlled with medication (phenobarbital) and did not recur. One child experienced a single seizure but was not diagnosed with epilepsy. Another child experienced absence seizures, and is treated with an anti-convulsant. Another child had a single febrile convulsion at 18 months. Another child had tonic-clonic seizures (stiffness followed by rhythmic jerking) between the ages of 8 and 14 years.

■ Hernias and minor genital problems

Nearly every male in this group had some minor unusual feature of the genital area; none of the females was affected. Among the anomalies noted among the boys and men were an overtight foreskin that needed circumcision; incorrect positioning of the hole usually at the end of the penis on the underside (hypospadias) - this is repaired surgically; undescended testicles on one or both sides, in one case persisting despite surgical correction; abnormally small testes and in one case a partial rearrangement of the penis and scrotum with the penis overlying.

One child also had inguinal hernias (in the groin), repaired surgically.

■ Heart

Most children were born with a healthy heart but two children are known to have had a heart condition at birth. In one case, there was a very large patent ductus arteriosus (PDA, a persisting structure of the fetal circulation) and an enlarged pulmonary artery (the vessel taking blood to the lungs). Another baby had a hole between the lower two heart chambers (ventricular septal defect, VSD) that was closed surgically at one year. Heart conditions need monitoring and may need surgical correction.

■ Temperature control

Two children have experienced very high temperatures (to 41°C/ 106°F) that required control with medication. Only two children are known to have had repeated respiratory infections, requiring adenoid and tonsil removal in one child who still has marked mucous congestion at 14 years.

“ When she is ill or feverish, she will sometimes not want to eat or drink because of a sore throat, so she is hospitalised for failure to thrive ” - 14q32.1 or q32.2 deletion, age

13 years

Other

A broad variety of other problems have been seen at birth, including in one baby an imperforate anus (the opening at the end of the rectum is missing so stools cannot leave the body properly) and a deep sacral dimple (a dimple at the end of the spine) and in another a marked weakness of the diaphragm, the muscular wall that keeps the contents of the abdomen separate from the chest. This baby also had abnormal drainage tubes in the urinary system and was diagnosed with diabetes insipidus, a condition in which too much urine is produced due to low levels of the antidiuretic hormone vasopressin or an abnormal response in the kidneys to this hormone. In another baby, one kidney was placed abnormally low but we do not know about its function. One child with a deletion within band 14q31 developed hypothyroidism, and was treated with daily thyroxine replacement.

Outlook

The outlook for any individual baby is determined by any clinical problems that are found. The evidence from this series is that many babies and children thrive into adulthood and even old age, as a number of adults have been described, one aged 62 years and another a grandfather.

Development



7 months old