

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 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 Oliver Bartsch, Institute of Human Genetics, Mainz, Germany and by Professor Maj Hultén BSc PhD MD FRCPATH, Professor of Reproductive Genetics, University of Warwick, UK 2007. (PM)

Copyright © Unique 2007

Rare Chromosome Disorder Support Group Charity Number 1110661

Registered in England and Wales Company Number 5460413



16p13 deletions



rarechromo.org

Sources

The information in this leaflet is drawn partly from the published medical literature. The first author and publication date of the key references are given on page 3 to allow you to look for the abstracts or original articles on the internet in PubMed. The leaflet also draws on Unique's database which contains regularly updated information. As well as three members with a pure 16p13.3 deletion, Unique has three members with the deletion and a change in another chromosome arm.

16p deletions

A chromosome 16p deletion means that a part of one of the body's chromosomes has been lost or deleted. If the missing chromosome material contains important instructions for the body, developmental delay, some learning difficulties and health problems may occur. How important these problems are depends on how much of the chromosome has been lost and where the deletion is.

Genes and chromosomes

Our bodies are made up of billions of cells. Most of the cells contain a complete set of tens of 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'. Apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy) the chromosomes are numbered 1 to 22, from largest to smallest.

Each chromosome has a short arm (at the top in the diagram) called p from *petit*, the French word for small, and a long arm called q (at the bottom). In a 16p deletion, material has been lost from the short arm of one of the two chromosome 16s.

Looking at 16p13

You cannot see chromosomes with the naked eye, but if you stain them and make their image about 1,000 times larger, you can see under a microscope that each one has a pattern of light and dark bands.

In the diagram on page 3 you can see that the bands are numbered outwards from the point where the short arm meets the long arm (the **centromere**). In a 16p13 deletion, the chromosome has broken in one or two of the five bands at the top of the diagram – 16p13.11, 16p13.12, 16p13.13, 16p13.2 or 16p13.3. The chromosome may break in two places with the 'sticky' broken ends rejoining but leaving out the chromosome material between them. This type of deletion is called **interstitial**. The other possibility is that the chromosome has broken in one place so the end is lost. This type of deletion is called **terminal**. When the deletion is close to the tip of the chromosome (known as the **telomere**), it is sometimes called a **subtelomeric** deletion.

The missing piece of chromosome can be tiny or much larger. If it is large enough to be visible when magnified under a microscope, it is called a **deletion**. Sometimes it is so tiny that it can only be identified using new technology with molecular tests such as FISH, MLPA (multiplex ligation-dependent probe amplification) or array-CGH. It is then called a **microdeletion**. Smaller deletions generally remove fewer genes and molecular techniques can show whether particular genes or parts of genes are present or not.

Why did the 16p13 deletion occur?

Some 16p deletions are the result of a rearrangement in one parent's chromosomes. This is usually a balanced translocation in which material from two chromosomes has swapped places but no relevant material has been lost or gained so the parent usually has no difficulties with health or development. A blood test to check the parents' chromosomes will show what the situation is.



A balanced translocation

Most 16p13 deletions occur when both parents have normal chromosomes. The term that geneticists use for this is **de novo** (dn). De novo 16p13 deletions are usually caused by a change that has 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 sometimes leads to problems.

Here is one possible scenario: during the formation of the egg and sperm cells the two members of each pair of chromosomes normally line up together and then break and rejoin to create new chromosomes. These new chromosomes contain different combinations of the genes passed down by the grandparents to the parents of the child. It is believed that after the chromosomes break, the rejoining can take place between the wrong broken ends, and this could lead to a 16p13 deletion. However, nobody has ever seen this happen, so it is still only an idea.

The breaking and rejoining is part of a natural process and as a parent you cannot change or control it. Children from all parts of the world and from all types of background have 16p13 deletions. No environmental, dietary or lifestyle factors are known to cause them. There is nothing that either parent did before or during pregnancy that can be shown to have caused the deletion to occur or prevented it.

Can it happen again?

The possibility of having another pregnancy with a 16p13 deletion depends on the parents' chromosomes. If both parents have normal chromosomes, the 16p deletion is very unlikely to happen again. If a blood test shows that either parent has a chromosome change involving 16p, the possibility is increased of having other pregnancies with chromosome changes. Once the family chromosome change is known, a test can be done in any future pregnancy to find out whether the baby's chromosomes are affected. Discussing the chromosome change with other family members gives them the opportunity to have a blood test to see if they too carry it. A genetic specialist can give you more guidance for your family.

Will my child with a 16p13 deletion have similarly affected children?

Adults with small 16p13 microdeletions may form close relationships and want to have children. We have not known about the condition for long enough to be certain if it affects fertility but it is likely that fertility will be normal. In each pregnancy, someone with the deletion has a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the deletion. Their ability to look after a child is very likely to be closely related to their own degree of learning difficulty.

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, if variable delay in hand use and fine motor skills. This delay means that early intervention by occupational therapy to stimulate hand use is vital. In one child, personal care and feeding was delayed because of weakness and shakiness, but wearing thumb splints was helpful. In another, the pincer grip was not evident until five years.

How will communication be affected?

Children will generally be slower to understand and express themselves in speech and may be helped by learning to sign their needs or by assistive communication systems and devices. In general, it appears that the use of language reflects children's learning ability. There is some evidence both in the medical literature and within *Unique* that children face particular difficulties with articulation and clarity. Receptive language (understanding) appears to be generally in advance of expressive language (speaking). Before words emerge, children generally supplement signing with gestures and vocal noises. Progress from single words to phrases and sentences is also likely to be delayed, but one six-year-old was talking in full sentences, although individual sounds and initial consonants in particular remained unclear.

How can a child's ability to learn be affected?

Children with a 16p13 deletion can be expected to need some support with their learning but the amount of support needed cannot be reliably predicted simply from the chromosome make-up.

A child with a small terminal 16p deletion close to the tip of the chromosome may have no learning difficulties or only slight problems. Where the deletion is larger, learning difficulties are more likely and may be more marked. Recorded IQs of individuals range between 53, 65, 76, 70 and 88 and where no IQ has been recorded, both children and adults have been described as of markedly lower ability than other members of their family. The experience of *Unique* is that learning difficulties may be more marked than this analysis suggests.

While there are children with a 16p13 deletion who attend mainstream (regular) schools with appropriate support, the special needs of others, probably the majority, are better met in an environment that caters for them specifically.

Outlook

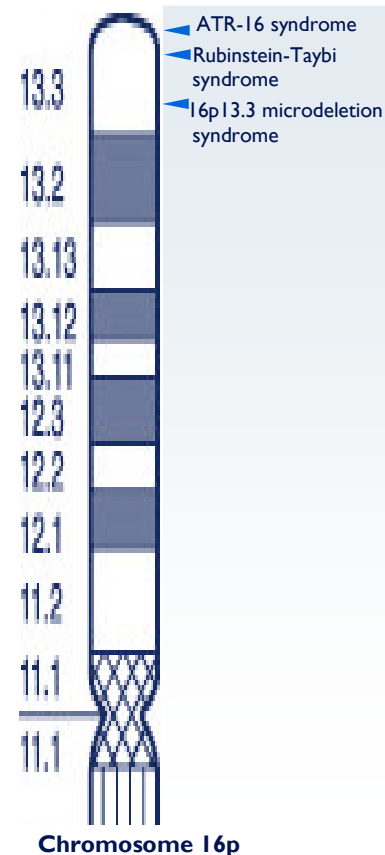
A child's outlook depends as much on their developmental profile and any clinical problems as on their chromosome make-up. In some cases children have been slow to acquire the personal care skills that will underpin eventual independence. In others a measure of supported independence seems likely.

The karyotype

Your genetic specialist can tell you more about what chromosome material has been lost. You will almost certainly be given a **karyotype**, a shorthand code that shows the bands where the chromosome has broken and rejoined. A band can contain many genes and depending on the technology used to find your child's chromosome deletion, the karyotype sometimes shows whether particular genes are present or not. 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. But some features and health problems are similar in people with a 16p deletion. This leaflet describes the things that are similar.

References

Bartsch 2006; Viprakasit 2003; Wiley 2003; Daniels 2001; Horsley 2001; Lindor 1997; Lamb 1993; Wilkie 1990; Hutz 1986; Bowcock 1984/Borochowitz 1970; Weatherall 1981



The end of chromosome 16p is rich in genes. At least 20 known genes in this region direct functions including developmental pathways and production of haemoglobin, the oxygen-carrying molecule in blood. In particular, there are three syndromes associated with deletions from 16p13.3. They are:

- Loss of material from the very end of the short arm of chromosome 16 is believed to generally result in a condition known as **ATR-16 syndrome**. ATR stands for alpha thalassaemia retardation and 16 refers to chromosome 16. The main feature of this syndrome is an increased risk of being born with a blood disorder known as haemoglobin H disease or alpha thalassaemia. A mild to moderate degree of learning difficulty is also typical, depending on the size of the deletion. Other features depend on what chromosome material and genes have been lost.
- Loss of part of the 16p13.3 band further from the end of the arm results in a condition known as **Rubinstein-Taybi syndrome**.
- Some babies born with Rubinstein-Taybi syndrome are more severely affected and seem to be prone to very severe infections. Early evidence suggests that they have lost additional genes. These babies are believed to have an emerging syndrome known as **16p13.3 microdeletion syndrome**.

ATR-16 syndrome: most common features

The main symptoms of ATR-16 syndrome are a blood disorder and usually mild to moderate learning difficulties. However, small deletions around the genes whose absence causes the blood disorder can leave no other effects at all (Horsley 2001). Babies may also have some unusual facial features, but these are not typically very distinct. They include widely spaced eyes, hooded eyelids (ptosis) and a wide forehead. Since ATR-16 syndrome is caused by the loss of chromosome material, larger deletions mean that more genes have been lost and the effects are generally more obvious.

Blood disorders in ATR-16 syndrome

Haemoglobin is the substance in blood that carries oxygen and iron around the body and gives blood a red colour. Low levels of haemoglobin cause anaemia. In children with a 16p deletion, genes that are important for the production of haemoglobin may be lost, causing a blood disorder. The genes on 16p that are important for haemoglobin production are called alpha globin genes and children usually inherit two of them (known as alpha-1 and alpha-2) from each of their parents, so they have four alpha globin genes in all. A child with a 16p deletion which includes these genes will only have two alpha globin genes. This causes a blood condition called alpha thalassaemia trait. Although the blood of someone with alpha thalassaemia trait has a slightly lower level of haemoglobin than usual, this does not usually cause any problems and they do not need to take extra iron unless prescribed by a doctor.

Some children with a 16p deletion have a 'double hit': on one chromosome 16 they have no alpha globin genes and on the other chromosome 16, they only have one. This causes a disorder known as haemoglobin H disease. Babies with haemoglobin H disease usually make enough haemoglobin for normal life but their red blood cells have less pigment than usual. They generally have a moderate but stable degree of anaemia.

In terms of outlook, they have a normal lifespan. In some children with a 16p deletion who have haemoglobin H disease, the genes are intact but the chromosome deletion may have removed gene regulators from close by (Daniels 2001; Lindor 1997; Lamb 1993).

Further information is available from the Northern California Comprehensive Thalassemia Center website at www.thalassemia.com and in the United Kingdom at www.sickle-thalassaemia.org

Rubinstein-Taybi syndrome

In babies and children with a 16p13 deletion, a disorder known as Rubinstein-Taybi syndrome is caused by a change in a gene known as *CREBBP* (CREB binding protein; also called *CBP*) from 16p13.3 or by the loss of all or part of the gene. A genetic cause for Rubinstein-Taybi syndrome in most other people who do not have a 16p13 deletion has not yet been identified but in about three per cent of people with the syndrome a change in another gene named *EP300* (gene for p300 protein, located on chromosome 22q) has been found.

together. When the 16p13 end switches to the short arm of chromosome 8, with a break point at 8p11, there is a heightened risk of developing a type of leukaemia known as AML (acute myeloid leukaemia) due to the fusion of two genes (*CBP* on 16p13 and *MOZ* on 8p11). AML is treated with chemotherapy drugs.

Other concerns

Teeth

Teeth have been observed to be crowded in two children out of four.

Eyesight

The eyes in children with a 16p13.3 deletion are usually structurally normal. However, hooded upper eyelids (ptosis) are common a child with ptosis will need assessment to ensure that the drooping eyelid does not interfere with vision and the development of normal eyesight. If it does, it can be corrected surgically. Strabismus (squint) and amblyopia (lazy eye) may also occur. Depending on the cause and severity, treatment may consist of patching, exercises, prescribed glasses and if necessary surgery.

Hearing

Hearing is usually normal, although young children with and without a chromosome disorder are vulnerable to the conductive hearing loss caused by glue ear and relieved in long-lasting, severe cases by inserting aeration tubes into the eardrum.

Development

Most babies and children show a degree of developmental delay and benefit from early intervention with stimulation and play schemes. The extent of any delay varies from child to child and it is better to let your child show his own pace of development than to try to predict it in advance. Your children's centre, developmental paediatrician, opportunity playgroup, portage scheme and health visitor are resources you can turn to for ideas on suitable stimulation.

Sitting, moving: gross motor skills

Babies and children with a 16p13 deletion typically face some delay in reaching their mobility milestones but in general the delay is not usually more than moderate. From current information, babies acquired the skill of rolling over between six and 13 months; were able to sit between eight and 10 months; they became mobile in the six months after their first birthday and were walking by their second birthday or fairly soon afterwards.

Underlying some of the delay is a difficulty with muscular coordination which may make walking uneven and unsteady. A low muscle tone, making a baby or child feel unusually floppy to hold and making the joints very flexible, appears to be less common, although two *Unique* members needed supports or support boots to stabilise their ankles for walking.



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.

Is there a typical growth pattern?

There does not appear to be any typical growth pattern for youngsters with a terminal 16p deletion and children may be short, average height or tall. This is in contrast to youngsters with Rubinstein-Taybi syndrome who are typically short, although they grow at a normal rate in the womb before birth. The most typical body build appears to be thin, but at least one child became overweight by adolescence.

Medical concerns

Other medical conditions affecting individual members of *Unique* or reported in the medical literature include

- A heart condition in 3/12 children. One boy was born with a persistent ductus arteriosus (a persisting structure of the fetal circulation) that was corrected at five months; one baby had a defect that led to heart failure but was surgically repaired; and one was born with a complex of structural anomalies including coarctation (narrowing) of the aorta (vessel that takes blood from the heart to the rest of the body), a persistent ductus arteriosus, holes between the upper and lower heart chambers (known as atrial/ventricular septal defects or ASD/VSD), double-outlet right ventricle (where both the main vessels lead from the right side of the heart instead of both the left and right sides), requiring complex multi-stage repair surgery (Daniels 2001; *Unique*)
- Underdevelopment of the left lung at birth. The size difference disappeared by 18 months of age
- Frequent urinary tract infections
- Syringomyelia (development of a fluid-filled cavity within the spinal cord); the usual treatment is surgery
- Hernias in the groin, usually needed correction by surgery
- Seizures.

Tuberous sclerosis

A gene called *TSC2*, found at 16p13.3, is known to cause tuberous sclerosis when it is deleted or mutated. Tuberous sclerosis is a multi-system disorder in which tumour-like lesions occur in the brain, the skin and other organs and is often associated with seizures and a degree of learning difficulty. In a small number of children who lose the *TSC2* gene, a neighbouring gene (*PKD1*) that encodes a type of kidney disease is also lost. The consequence of this is the growth of cysts within the kidneys and a progressive type of kidney disease that leads to renal failure. Although it is known that a small number of people with tuberous sclerosis have a 16p13 deletion, no-one in *Unique* has developed tuberous sclerosis.

Malignancies

In rare cases, a balanced translocation occurs between the 16p chromosome tip and another chromosome arm. Swapping round chromosome material can bring genes together that are normally harmless but can become harmful when they are close

Most common features of Rubinstein-Taybi syndrome

- A variable degree of learning difficulty, usually moderate to severe, mild in some
- Short stature, following normal birth weight
- Broad and sometimes angulated thumbs and big toes
- Microcephaly (a very small head)
- Characteristic facial features, including skinfolds across the inner corner of the eye; arched eyebrows; a prominent beaked nose with small nostrils with the fleshy division between them (columella) lower than the nostrils; eyes that slant downwards and are apparently widely-spaced, with long eyelashes; unusually shaped and positioned ears; and a birthmark known as naevus flammeus. The typical facial features can vary with age
- Possible involvement of many organs, including the heart, kidneys, eyes, brain
- Possible feeding difficulties in babies, hearing problems, constipation, seizures
- Hypotonia (low muscle tone, so the baby feels floppy at birth)
- Undescended testicles in boys
- Usually sociable and friendly temperament

Living with Rubinstein-Taybi syndrome

Guidelines for the medical care of babies, children and adults with Rubinstein-Taybi have been developed at the Cincinnati Children's Hospital Medical Center in the United States. The chief recommendations are similar to the general recommendations for children with a chromosome disorder: at diagnosis, children should have a developmental assessment and an early reassessment if any signs of regression occur; a heart work-up that would include an electrocardiogram, an echo (scan) and examination by a paediatric cardiologist; a thorough assessment of eyesight by a paediatric ophthalmologist at diagnosis or by six months of age if diagnosed in the newborn period; an ultrasound of the kidneys; and a hearing test.

Further guidelines cover heart care; giving an anaesthetic; dental care; skin care due to the tendency to form keloids (an overgrowth of fibrous scar tissue after a wound); care of the nails due to a tendency to ingrowing toe nails and whitlows (paronychia); annual hearing tests; feeding support and readiness to actively treat babies with reflux or constipation; annual vision screening with early evaluation of any signs of glaucoma (raised pressure within the eye) or opaque area of the cornea at the front of the eye; surgical interventions to treat those children whose thumbs are significantly angulated or whose big toes have a duplication; regular orthopaedic review to check for joint problems and, from the age of 10 years for signs of spinal curvature; evaluation of sleep abnormalities and of frequent upper respiratory tract infections.

Families are encouraged to learn about their rights to early intervention and specific therapies to optimise their child's opportunities and minimise the effects of developmental delay. Other recommendations cover behaviour difficulties and, in adults, mood disorders.

Further information and support for families is available from the Rubinstein-Taybi Syndrome Association website at www.rubinstein-taybi.org and in the United Kingdom at www.rtsuk.org

(Hennekam 2006; Wiley 2003; Taine 1998; Wallerstein 1997; Breuning 1993; Hennekam 1993)

Is there a 16p13.3 microdeletion syndrome?

Recently, a group of researchers has identified three babies with a 16p13.3 deletion and a particularly severe form of Rubinstein-Taybi syndrome, with severe complications. They have named this the **16p13.3 microdeletion syndrome** and believe it is caused by loss of the *CREBBP* gene implicated in Rubinstein-Taybi syndrome as well as at least one other neighbouring gene, known as *DNASE1*. However, this information must be provisional until more babies with this deletion have been studied. When a new syndrome is first described, it is sometimes called an **emerging syndrome**.

The uncertainty means that if your baby is found to have a deletion from 16p13.3, your genetics expert will probably recommend using molecular genetic techniques to assess as precisely as possible the amount of chromosome material lost. This will make it easier for your child's doctors to give you helpful information about your baby's outlook (Bartsch 2006).

Emerging 16p13.3 microdeletion syndrome: most common features

- Severe features of Rubinstein-Taybi syndrome
- Increased risk of having serious anomalies of major organs including the heart or kidneys
- Vulnerability to infections
- Feeding difficulties as a baby and failure to thrive

(Bartsch 2006)

The Unique experience

In addition to these syndromes, three reports from *Unique* of children with a pure 16p13 deletion with no involvement of another chromosome arm show the following effects.

At birth

One baby was born a month early after a normal pregnancy and one was born at term. The babies' condition after birth was determined by their clinical problems: the baby born at term had a complex heart condition that was initially surgically repaired at four weeks of age, while the baby born early had many of the problems associated with prematurity. Both babies were reluctant feeders in the newborn period.

Minor anomalies of the **genitals** are often seen in babies with a chromosome disorder, especially in boys. In boys with a terminal 16p deletion, the testicles may not have descended into the scrotum at birth. The testicles may descend later or may be brought down and anchored in the scrotum in a surgical operation performed in early childhood. A mild degree of hypospadias may occur, where the hole that should be at the end of the penis is on the underside instead. If necessary, the hole can be re-sited in a surgical operation usually performed in the toddler years. In one girl, the lips of the vagina were fused at birth but this resolved with the application of oestrogen cream.

One baby with a terminal deletion from 16p13.3 had a cleft lip and palate that needed surgical repair.

Appearance



At 22 months (left); seven years (right)

Children with a very small deletion may show little facial sign of any disorder.

Individuals are not usually considered to resemble each other although the eyes may be widely spaced and there may be a subtle facial asymmetry. The upper eyelids may be hooded (ptosis). One family reported that their baby has a flat, wide nasal bridge, full lips and ears that are slightly low set and tilted.

Hands and feet

Various anomalies of the hands and feet, such as incurving fifth fingers, are relatively common in children with chromosome disorders. In children with a 16p deletion, anomalies of the hands are usually cosmetic and do not need treatment. However, children with Rubinstein-Taybi syndrome who have angulated thumbs and big toes may benefit from surgical correction.

Unusually angled feet (club foot, talipes equinovarus, in which one foot or both points downwards and inwards) occur in quite a few children and affect one *Unique* child. Correction of talipes depends on the severity and treatment ranges from physiotherapy and regular exercises to splinting, plaster casts and surgery. Webbed toes and clawed toes have also been seen, as well as a repeated tendency for the nail of the great toe to fall off.

What about food and eating?

Information on feeding in babies with a 16p13.3 deletion is scant, but in general young babies with a chromosome disorder frequently have feeding difficulties. None of the babies in this group breastfed successfully. In one *Unique* baby, the feeding problems have been troublesome and long-lasting and have been accompanied by severe constipation, although tube feeding was only needed for a week in the newborn period. In another baby with a heart condition feeding direct to the stomach continued at the age of 10 months alongside oral feeding with drinks and pureed foods.

Gastro oesophageal reflux (GORD, GERD), where the stomach contents return up the food pipe, is fairly common in babies with a chromosome disorder and affected both babies in this group. 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 passage