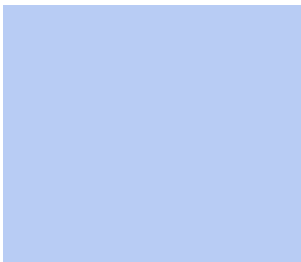


Unique

6p deletions



Sources

The information in this leaflet is drawn partly from the 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. You can also obtain abstracts and articles from Unique.

The leaflet also draws on the experience of Unique members. Of the fifteen members with a pure 6p deletion, nine have a terminal deletion (see right) and six have an interstitial deletion.

Eight families completed a detailed questionnaire in 2003/4.

References to this survey are characterised (U).

6p deletions

A 6p deletion is a rare chromosome disorder in which some chromosome material and genes have been lost from the short arm of chromosome 6. Like most other chromosome disorders, a 6p deletion increases the risk of certain birth defects, developmental delay and learning difficulties.

However, individual children vary a lot.

Chromosomes are the microscopically small structures in the nucleus of the body's cells that carry genetic information. Apart from the mother's egg cells and the father's sperm cells, there are normally 23 pairs of chromosomes in each cell of the body, making 46 in all. Apart from the sex chromosomes (two Xs for a girl and an X and a Y for a boy), they are numbered from 1 to 22, from largest to smallest approximately according to size.

Each chromosome has a short (p) arm and a long (q) arm that join at a centre known as the centromere.

Chromosomes can be stained so that each has a distinctive pattern of light and dark bands when viewed at about 1000 times life size under a light microscope.

Deletions from the short arm of chromosome 6 are rare. By 2005, around 30 people with the disorder had been described in published medical research. There are of course many more and when this leaflet was published, *Unique* had 21 members with a 6p deletion ranging in age from 42 to two years, of whom 15 had a pure 6p deletion with no other chromosome involved (Davies 1996; Chen 2004; Mirza 2004).

Different deletions

6p deletions are often divided into **interstitial** and **terminal deletions**. A terminal deletion is one where there is one break in the chromosome and the material is missing beyond the breakpoint. In an interstitial deletion, there are two breaks and the broken ends have rejoined, leaving out the intervening segment. In reality, there is considerable overlap between people with interstitial and terminal deletions and the specific breakpoints are the key information that will help a geneticist describe the possible effects.

Recently a new type of **subtelomeric terminal deletion** has emerged. Material has been lost from band 6p25 just below the end of chromosome but the amount is so tiny that it is invisible even under the highest powered microscope and can only be identified using a molecular technique such as FISH.

Common features

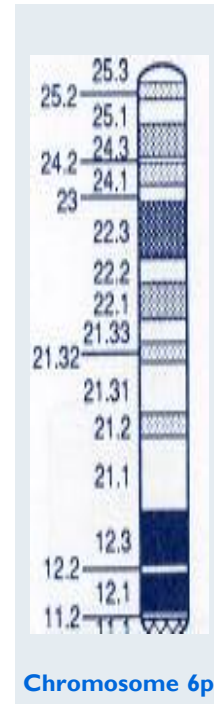
Certain features have been found to be common in groups of people with particular 6p deletions. In reality, there is considerable overlap between the groups. Individual children will differ from the group and can differ from another child with exactly the same deletion; as individuals, they may have some of these features or few of them and can be mildly or more obviously affected.

Common features of interstitial deletions

(Davies 1996; Chen 2004; Mirza 2004)

Breakpoints typically in 6p22~24 and p24~25

- Developmental delay and some level of learning difficulty
- Hearing impairment
- Defects of development of the anterior chamber (front portion) of the eye
- Anomalies of the brain
- Kidney conditions
- Heart conditions
- Cleft lip and / or palate (split in the roof of the mouth)
- Short neck
- Unusual hands, including incurved, webbed fingers or both



Chromosome 6p

Common features of terminal or subtelomeric deletions

(de Vries 2001, 2003; Anderlid 2003; Chen 2004; Mirza 2004; DeScipio 2005; Le Caignec 2005; Lin 2005)

The breakpoint is typically in 6p24 or 6p25. In some cases the deletion is invisible even at maximum magnification and is detectable only by a molecular technique such as FISH

- A level of developmental delay. This is variable and some children may have normal cognition
- Characteristic facial appearance, including wide set and downslanting eyes
- Hearing impairment
- Defects of development of the anterior chamber (front portion) of the eye
- Anomalies of the brain, especially Dandy Walker malformation (see page 7) or a variant
- Heart conditions

Other features include a cleft lip and palate, short neck, hernias, seizures, dental anomalies, spinal curvature and kidney anomalies.

Other deletions

There is very little formal information on people with deletions between band 6p22.1 and the centromere. At the time of publication, *Unique* had one member with a deletion from 6p12.2-p21.1 and an adult member with a terminal deletion with the breakpoint in 6p21 (see page 10).

Appearance

There are typical facial features associated with 6p deletion. They include wide set eyes with a downwards slant and sometimes skinfolds across the inner corner, a broad, low nasal bridge, low set ears with an unusual shape, a flat or prominent groove in the upper lip and a down turned 'tented' mouth with a thin upper lip without a Cupid's bow. In addition, the neck is typically short and may have excess folds of skin (Zurcher 1990; Palmer 1991; Davies 1999; Lin 2005).

Growth

Most babies are born a normal weight. However, a minority of babies are small for dates and may have suffered intrauterine growth retardation. One baby with a 6p23-p24.2 deletion who was growth retarded at birth grew well during the first year of life and then remained a normal weight. However, another baby with a 6p21.33-p23 deletion had a low birth weight and remained growth retarded. Babies with feeding difficulties or serious heart conditions face the possibility of slowed growth, although they may show catch-up after treatment. Other babies continue to grow slowly and remain short as children. One child with a 6p25 deletion responded well to growth hormone treatment, his height rising from the tenth centile to an age-appropriate level within two years (Jalal 1989; Zurcher 1990; Plaja 1994; Davies 1999; U).

“ I wanted to know what the diagnosis really meant for her life. I guess I still don't have the answer and I am glad no one said anything so I really have an open book and she is writing her own story. She is the one leading and we follow her way.”

Learning

A degree of learning difficulty is usual and some researchers suggest that this is usually moderate to severe. There is an assumption that small deletions confer fewer learning difficulties than large deletions but recent research has shown that this is not necessarily true. A 6-year-old girl and a 2-year-old girl, each with a 6p24 deletion, have recently been described as having normal learning ability as has a 13-month-old boy with a 6p23-p24.3 deletion and one girl with a tiny terminal deletion (Jalal 1989; Palmer 1991; Plaja 1994; Anderlid 2003; Chen 2004; Mirza 2004).

The evidence from *Unique* is that children face a very variable degree of learning difficulty. At one end of the spectrum are children with no discernible learning difficulties and a teenager with a 6p25-pter deletion with mild-to-moderate intellectual disability who has eight GCSEs, the examination taken in the UK at the age of 16; in the middle of the range is a boy with a terminal deletion from 6p24 with moderate learning difficulties who at the age of 8 could read five words, was aiming to recognise all upper and lower case letters and to add and subtract to 10; at the severe end was a 13-year-old girl operating at the level of a 3 to 4-year-old. Language and literacy skills appear to be more affected than number ability, but even the severely affected adults may learn to read well enough to consult a magazine and to tell the time. Children with mild learning difficulties may achieve well in a mainstream school with support, but most children do better in a specialist school.

Speech and communication

Speech and language are typically disproportionately delayed. This is usually explained by the hearing impairment but one child with good hearing had receptive speech skills ahead of her chronological age but a marked delay in expressive language. The child with the smallest recorded terminal deletion and unimpaired learning ability showed severe language impairment and difficulties in the social interaction of speech (Anderlid 2003).

Single words emerge typically between two and three years and two *Unique* members have a good command of intelligible language, although one needed both speech and confidence therapy to achieve this and other members showed greater confidence at home than at school. Most other members used a mixture of signing and speech. One adolescent was continuing to become more verbal through her teen years.

Reports in the medical literature show a two-year-old with speech and language at 16 to 18-month level; a 3 ½ year-old with a vocabulary of three single words; a 5-year-old with conductive hearing loss with a wide variety of single words; a 15-year-old using five or six phrases and an adult of 20 who first babbled at 36 months using single words and sign language (Jalal 1989; Zurcher 1990; Davies 1996; Law 1998; Davies 1999; Anderlid 2003; U).

“ Jake is very good at the computer, can go into the system and change the settings himself - Jake, at 10.

Sitting, moving, walking ...

There is great variation in mobility, although all children show some delay in reaching the standard milestones. There appears to be no obvious link between the size of the deletion or the breakpoint and the mobility skills that children achieve.

One *Unique* member with a 6p25 deletion did not sit alone until she was over 2 and only walked alone at 5, but at 13 was fully mobile and very active. Another, also with a 6p25 deletion, walked and cycled but could not co-ordinate the movements for swimming and had difficulty running and playing sports. She sat at 6 months and walked at 18 months. A 10-year-old with a 6p24 deletion who started slowly (sitting at 18 months, crawling at 3 and walking at 4) was ‘very mobile, runs, jumps, loves to swim with armbands, dance to any music and makes up all his own moves’. An eight-year-old with a 6p24 deletion needed a wheelchair for outdoor trips. Finally, a three-year-old with a 6p24 deletion ‘is pretty much like any other three year old. She can sit, walk, has just started jumping a few inches from the floor, she can kick a ball, throw a ball, go up and down the slide and loves water. She is not there yet with the tricycle but can get around. She loves dancing and has lots of rhythm.’

Reports in the medical literature show that **hypotonia** is typical of a 6p deletion and is usually noticeable from birth, persisting sometimes into adulthood. The level may be mild or severe the whole body is usually involved. Walking style may be unusual or clumsy and some children walk on their toes and never acquire easy mobility over uneven surfaces (Jalal 1989; Zurcher 1990; Palmer 1991; Davies 1996; Law 1998; Davies 1999; U).

Medical concerns

■ Eye problems

Eye problems are a common feature. This is thought to be due to the location of a gene in this region, called *FOXC1* (formerly called *FKHL7*), which plays an important role in eye development. Chromosome anomalies affecting 6p24-25 often result in abnormalities of the iris (the coloured part of the eye) which may include slightly eccentrically positioned pupils. Up to half of individuals with such eye changes develop glaucoma in future years; the rest do not. Those who do develop glaucoma, a condition in which the pressure in the eye can become raised, can be treated, usually with eye drops. It is recommended that all individuals with chromosome anomalies affecting 6p24-25 are examined by an ophthalmologist, to ensure that if treatment is needed, it is started promptly. On request, *Unique* can put you in touch with an ophthalmologist with a particular interest in this area, who could facilitate local follow-up for you.

Other eye anomalies that are occasionally seen include: grey-blue colouring of eyeball (possibly associated with a loss of chromosome material at 6p24-p25), microphthalmia (smaller eyes), strabismus (squint, where the eyes are convergent or divergent) that may recur after surgery, prominent epicanthic folds (folds of skin across the inner corner of the eye) and refractive errors requiring correction (short or long sightedness) (Lehmann 2002; Mirza 2004).

■ Hearing impairment

Hearing impairment is relatively common and may progress with age. The suspected cause is the absence of an as yet unidentified gene at 6p24-25, near *FOXC1* but almost certainly closer to the end of 6p. The progressive nature of the hearing loss means that it is good practice for hearing checks to be repeated at six-monthly intervals in early childhood. The loss may be either conductive (caused by an obstruction that stops sound reaching the inner ear) or sensorineural (caused by damage to the inner ear, the auditory nerve or the nerve pathways in the brain), or mixed (Zurcher 1990; Davies 1999; Anderlid 2003; Mirza 2004).

Severity of hearing impairment ranges from mild to severe enough for hearing aids to be needed and education to be needed in a school for the deaf (25 to 70 decibels, progressing to 70-100 decibels in adulthood). Hearing loss may not be identified early, leading to unnecessary disability (Law 1998; Anderlid 2003).

Five out of seven *Unique* members reported hearing impairment and it was possible in a sixth. Additional features were a relatively high rate of tympanic (eardrum) perforation (three out of five), in two children requiring patching, and a high rate of hearing aid use (four out of five). One child was found to have a structural anomaly of the inner ear (immobile anvil) during surgery to patch the eardrum (U).

■ Heart conditions

Once a 6p deletion has been diagnosed, a child can expect to have a thorough cardiac evaluation. Heart conditions are common in babies with either interstitial or terminal deletions. Persistent ductus arteriosus (PDA, in which a channel between

the aorta (the blood vessel that leads from the heart to take blood around the body) and the pulmonary artery (the blood vessel that takes blood to the lungs) fails to close as normal shortly after birth), septal defects (holes in the muscular walls between the two sides of the heart) and bicuspid aortic valve (absence of a third flap or valve in the aortic valve that regulates blood flow from the heart into the aorta) occur fairly frequently. Other heart conditions described include double outlet right ventricle (the blood vessels leading from the heart to the lungs and around the body both arise from the same (right) side of the heart; patent foramen ovale (PFO, where an opening known as the foramen ovale that usually closes after birth stays open instead); and a marked narrowing (coarctation) of the aorta. Absence of the *FOXC1* gene from chromosome 6 is believed to be a key factor in abnormal aortic valve development but genes in other regions of chromosome 6 closer to the centromere are thought to contribute to the other typical heart conditions. It has been suggested that a gene called *BMP6* situated at 6p23-p24 is the most likely candidate (Palmer 1991; Plaja 1994; Davies 1996; Law 1998; Davies 1999; Anderlid 2003; Mirza 2004; U).

Heart conditions among the 50 per cent of *Unique* members who were affected either resolved on their own or were successfully treated with surgery. Before treatment, the heart defects led in some children to diminished feeding and suppressed growth as well as to diminished energy and activity levels.

■ Head and brain

Head imaging may be recommended for your child because a variety of structural anomalies of the brain have been found in some children with 6p deletions. One anomaly is known as Dandy-Walker and involves the cerebellum (an area at the back of the brain that controls movement) and the fluid filled spaces around it. This may in some cases be associated with hydrocephalus (a build-up of fluid within the brain). It has been observed that Dandy-Walker on its own was not associated with severe developmental delay, but hydrocephalus added to the problems. In terms of the skull, the fontanelles (soft spots) and joins between the cranial bones may fuse late, with closure of the front fontanelle reported as late as 32 months.

Cleidocranial dysplasia

People with deletions that include the part of band 6p21 that contains a gene known as *CBFA1* may have signs of cleidocranial dysplasia, a condition that affects the teeth, the collar bones and the bones of the skull. In typical cleidocranial dysplasia, there are wide gaps between the skull bones, underdeveloped or – very occasionally - missing clavicles (collar bones) and abnormal tooth development, with normal milk teeth, delayed permanent teeth and impacted extra teeth. However, many people do not have the full form of the condition.

The shape and size of children's heads is variable, with unusually small or large heads both observed. Various head shapes have been noted – long, broad or triangular - and the back of the head is variously reported to be flat and wide (Jalal 1989; Zurcher 1990; Palmer 1991; Plaja 1994; Davies 1996; Davies 1999; Mirza 2004,2; Lin 2005; U).

■ Lax or dislocated joints

There is increasing evidence that easily dislocated joints may form part of the typical terminal 6p deletion syndrome. A number of children have been reported in the medical literature and this is supported by the experience of *Unique* members. Of the three reports in the literature, one child had dislocated hips, knees, elbows and shoulders and unusually angled feet (club foot); a second had dislocated wrists and knees and out-turned feet; a third had dislocated ankles and unstable hips, knees, shoulders, wrists and fingers. Five out of eight *Unique* members remarked on some joint instability or disease: one child had easily dislocatable hips and wore orthopaedic support boots; another was reported to have hyperlax joints and wore ankle braces; another dislocated the radial head of his right arm and was reported to have hypermobile and very flexible joints; a fourth was treated for juvenile arthritis. Finally, one girl had Perthes disease, a disorder that disrupts the blood flow to the ball of the thigh head in the hip joint (Zurcher 1990; Palmer 1991; Mirza 2004; U).

Spine Two *Unique* families mentioned scoliosis. In one child it was severe enough to have persisted despite bracing and plaster jackets and to require surgery; in another it was mild enough to be helped by chiropractic (U).

■ Kidney conditions

Kidney conditions have been reported as typical and problems described include an obstruction at the junction of the kidney and the tube that takes urine to the bladder (ureteropelvic junction) causing a build-up of urine and enlargement of the kidney (hydronephrosis), sometimes observed antenatally; large, cystic right kidney; absent kidney (Palmer 1991; Davies 1996; Davies 1999; Suwanrath-Kengpol 2004; U).

Genital anomalies are reportedly common and varied, although not among *Unique* members. In girls the only unusual feature noted is wrinkled labia majora, while in boys the following features are recorded: bifid scrotum over penis (the scrotum is divided and the penis is below it rather than above); vertical groove at penis tip; micropenis (a very small penis); hypospadias (the hole usually at the end of the penis is on the underside instead); small genitalia in an adult. In addition it is relatively common for the testes to be undescended at birth (Jalal 1989; Palmer 1991; Plaja 1994; Law 1998; Davies 1999; U).

■ Cleft lip and/or palate

Anomalies in the midline of the facial structures that have been seen in children with a 6p deletion include a cleft (split) on one or both sides of the upper lip, a defect in the upper jaw, and a split in part of the roof of the mouth or the uvula, the finger-like piece of tissue that hangs from the back of the soft palate. Palate anomalies have functional as well as cosmetic consequences. A high palate is typical and often affects feeding.

One gene involved in cleft lip and palate, possibly the *AP-2* gene, has been mapped to 6p24.3; more than one gene in the 6p24-p25 region may be involved. Cleft lip and palate are correctable with surgery; meanwhile specialised feeding support should be available (Jalal 1989; Palmer 1991; Plaja 1994; Law 1998; Davies 1999; Mirza 2004; U).

Teeth The teeth may be crowded and incorrectly positioned due to disruption to the development of the jaw and its small size. In addition, teeth may have marked enamel defects. See also Cleidocranial dysplasia (page 7) (Jalal 1989; Mirza 2004,2; U).

■ Hands and feet

Unusual features of the feet that have been described include flat feet, club foot (talipes), different-sized feet, metatarsus adductus (the front half of the foot turns inwards), rocker bottom feet with abnormal toes, short big toes, overriding toes, a large 'sandal gap' between the 1st and 2nd toes, long second toes, short toes and underdeveloped toe nails.

Unusual features of the hands include incurved 5th fingers, overlapping fingers, short final joints and short fingers (Jalal 1989; Zurcher 1990; Palmer 1991; Davies 1996; Davies 1999; Anderlid 2003; Mirza 2004; U).

■ Skin

Dry skin and eczema are mentioned frequently in both published medical research and by *Unique* members. Dry skin may develop in early babyhood and require steroid treatment. Loss of the desmoplakin *DSP* gene at 6p24 may be a contributory factor but is not enough on its own to cause skin defects. One *Unique* member also has psoriasis (Law 1998; Davies 1999; Mirza 2004; U).

A child with a 6p deletion of Hispanic parents has been described as atypically fair-skinned (Mirza 2004, 2).

■ Hernias

Abdominal hernias have been commonly described in the medical literature, although this experience is not reflected in the *Unique* membership. Most of those mentioned in research reports are small and umbilical (at the navel, belly button) or inguinal (in the groin) and can be simply corrected with surgery (Davies 1996; Law 1998; Davies 1999).

■ General health and wellbeing

As newborns and in early babyhood, babies tend to have frequent respiratory infections, with occasional hospitalisations for pneumonia and asthma. Narrowing of the trachea (wind pipe) requiring a tracheostomy (a tube to allow air and oxygen to reach the lungs) has been described (Palmer 1991; Davies 1996; U).

■ Puberty

We are only aware of two accounts of puberty in people with 6p deletions, one showing normal development in a boy and one in the *Unique* survey, showing normal puberty with periods starting at 12 years in a girl (Law 1998; U).

*“ Laura is a generous person who delights in giving and puts a tremendous amount of time and thought into selecting the right gift. She has taught me we are all unique
– Laura, at 19.*

*“ Gordon is an affectionate, fun loving young man, who is full of energy. He has no sense of danger so this keeps us on our toes and thus keeps us young!
– Gordon, at 24.*

Independence

The *Unique* survey showed great variation in acquisition of the skills that underpin independent living. While one *Unique* member with a 6p25 deletion was learning to drive and attending to all her own personal care, another 24-year-old with a 6p21 deletion needed help with every aspect of daily care. Personal care skills increased throughout childhood but nearly all people, if not all, would expect to need some supervision and support in their adult lives. Some babies had initial feeding problems, but there was no clear pattern and by middle childhood feeding did not appear to be a problem.

Reports in the medical literature have rarely described adults. However, a 32-year-old man with a 6p24.3-pter deletion worked for 10 years as a machine operator in a factory, lived with his parents and was able to drive a car (Law 1998; U).

Behaviour

Two distinct behavioural patterns emerged from the accounts of *Unique* members. On the one hand, children could be intensely shy, anxious and lack in self confidence. They could get easily overwhelmed and flustered. This trait was seen in people of all abilities but might appear in isolation in children with mild learning difficulties.

Children who were frustrated and unable to express their needs could react aggressively and even violently. This by no means affected everyone, but was seen in around half of *Unique* members. In some, it was limited to violent gestures and outbursts; other children might get so frustrated that they bit themselves and others. Children could also be extremely sociable and very friendly.

Reports so far in the medical literature have paid scant attention to behaviour. A 28-month-old toddler with a 6p24pter deletion is noted to have age-appropriate personal and social skills; a 4-year-old child with no intellectual disability and a tiny terminal deletion showed impaired social interaction in speech; a 20-year-old man had marked behaviour problems with dislike of being touched and aggressive episodes (Zurcher 1990; Davies 1999; Anderlid 2003; U).

“ Harry is very loving, has his own personality and likes to be popular. He is very comical and likes to entertain people. He is very clever and knows his own mind – Harry, at 8.

How did this happen?

Rearrangements occur in chromosomes as part of evolution. They affect children from all parts of the world and from all types of background. They also happen naturally in plants and animals. So there is no reason to suggest that parents' lifestyle or anything that they did caused the loss of chromosome material.

Changes to the structure of chromosomes such as 6p deletions occur most often during the cell divisions that lead to the creation of eggs or sperm. Each of the 46 chromosomes first doubles lengthwise into two strands that are held together at the point where the short and long arms meet, known as the centromere. The chromosomes then arrange themselves in 23 pairs, with pairs lying alongside each other. The two members of each chromosome pair 'recognise' each other because the DNA sequence ladder that comprises them is in a similar order. However, when a small region of DNA on a chromosome has a twin region of DNA located further down the same chromosome, the pair of chromosomes may not align correctly. Usually, after chromosomes pair, the members of a pair exchange segments of DNA with their pair-mates, in a process known as crossing-over (recombination). After this point, the chromosome strands repel each other but are held together at the cross-over points known as chiasmata. Deletions can arise during this process when the chromosomes have lined up incorrectly. An unequal cross-over means that the exchanges are not equal between the members of a chromosome pair. In this case, a piece of one chromosome can loop out and be lost from the middle of the chromosome (interstitial deletion) or from the end of the chromosome that then 'heals' (terminal deletion).

Why did it happen?

A chromosome 6p deletion can occur as a result of rearrangements in one parent's own chromosomes or, more often, it can happen out of the blue, so the child with the chromosome disorder is the only person in the family with rearranged chromosomes. It is then called a *de novo* rearrangement. The only way to know if the disorder is inherited or not is for the parents' chromosomes to be checked and the results explained by a geneticist or genetic counsellor.

If the check reveals a structural rearrangement of one of the parents' own chromosomes, this is usually balanced so that all the chromosome material is present, and the parent is then almost always healthy.

“ Gordon loves music and has a small accordion, drums and guitars. Although he doesn't play tunes he has a good sense of rhythm - Gordon, at 24.

“ Harry enjoys singing, the computer, his playstation and dancing; he is obsessed with car registration numbers - Harry, at 8.

“ Ana is very affectionate, independent and confident in herself. She is very popular among kids her age at daycare. She brings so much joy and light to our life. If someone could turn the clock back and I could change her diagnosis, I wouldn't do it - Ana, at 3½.



Support and Information

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This leaflet 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. The information is believed to be the best available at the time of publication and has been verified by Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, UK and by Dr Ordan J Lehmann, Associate Professor, Departments of Ophthalmology & Medical Genetics, University of Alberta January 2004. Literature updates added September 2005.

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