

UNIQUE

UNDERSTANDING GENES & CHROMOSOMES

2p deletions

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with a 2p deletion. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this condition.

"Everything she does is special. I could write an entire book on all the things she has contributed to our life. She is an absolute joy and blessing, and I can't imagine my life without her!"

A 2p deletion means that the cells of the body are missing a part of one of the 46 chromosomes, in this case part of chromosome 2. For healthy development, chromosomes should contain just the right amount of genetic material (DNA) – not too much and not too little. Like most other chromosome disorders, having parts of chromosome 2 missing increases the risk of a child having developmental delay, learning difficulties and anomalies at birth. However, the effects vary and depend very much on what genetic material is missing.

Chromosomes and genes

Chromosomes are structures found in the nucleus of the body's cells. Every chromosome contains 100s to 1000s of genes which can be thought of as individual instruction booklets (or recipes) that contain all the genetic information the body needs to develop, grow and function. Chromosomes (and genes) usually come in pairs, with one member from each pair being inherited from each parent.

We have 23 pairs of chromosomes, giving a total of 46 individual chromosomes. Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest, so chromosome 2 is the second largest chromosome. Each chromosome has a short or (p) arm (shown at the top of the diagram on page 3) which is joined to a long (q) arm (the bottom part of the chromosome) at a point known as the centromere.

Chromosome deletions

When a sperm cell from the father and an egg cell from the mother first join together, each carries just one member from each chromosome pair, so in the case of chromosome 2, just one chromosome 2. Together they form a single cell that now carries both chromosomes from the pair, so two chromosome 2s. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes can break off or become arranged differently than usual.

People with a 2p deletion usually have one intact chromosome 2, but a piece from the short arm of the other one is missing or deleted. Although the exact numbers and types of genes that are included in the deletion is often not known, since some genes are missing there can be effects on a person's learning and physical development. It is believed that any clinical difficulties are probably caused by having only one copy (instead of-the usual two) of a number of genes. But a child's other genes, environment and unique personality help to determine their future development, needs and achievements.

Chromosome 2



Looking at the short arm of chromosome 2 (2p)

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, it is possible to see that each one has a pattern of light and dark bands. In the diagram on 5 -10 the right you can see that the bands are numbered outwards from the centromere.

By looking at your child's chromosomes in this way, it is possible to see the point (or points) where the chromosome has broken and to see what material is missing, when the missing piece is large enough. If the amount of missing material is quite small, this type of routine analysis will not show it, or it will not be clear where the chromosome has broken. A deletion so small that it can't be seen through a microscope is known as a microdeletion. New, more sensitive molecular techniques such as fluorescent in situ hybridisation (FISH) or array comparative genome hybridisation (array-CGH, also known as microarrays) may be needed to detect or confirm very small 2p deletions.

If the missing piece is closer to the centromere, the deletion is called proximal. If it is closer to the tip of the short arm, it is called distal. Sometimes the chromosome breaks in two places, and the 'sticky' broken ends re-join, leaving out the chromosome material between them. You will sometimes see this type of deletion called interstitial. Sometimes the chromosome breaks in one place, and the broken end 'heals'. This type of deletion is sometimes called terminal because it includes the end (terminus) of the chromosome arm.

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 way of describing what the chromosomes look like. The karyotype often shows the bands where the chromosome has broken. 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. But you will usually need to ask your genetic specialist for a full explanation.

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 symptoms 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.



46, XY, del (2) (p11.2p13) dn

46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material has been lost
(2)	The deleted material came from chromosome 2
(p11.2p13)	The chromosome has broken in two places. The first break is at p11.2 and the second break is at p13, so these are the ends of the missing section. This is a proximal deletion
dn	The deletion has occurred de novo or as a 'new event'. The parents' chromosomes have been checked and no deletion or other chromosome change found at 2p11 or 2p13. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child.

As well as a karyotype or instead of one, you may be given the results of a molecular test such as array-CGH for your child. The results are likely to read something like the following example

46, XX.arr cgh 2p16.1p15(RP11-260K8->RP11-479F13) x1

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
.arr cgh	The analysis was by array comparative genome hybridisation (CGH)
2p16.1p15	This analysis showed two breaks in the chromosome, one in band 2p16.1 and the other in band 2p15
(RP11-260K8 ->RP11-479F13) x1	This shows the part of the chromosome that is present in one copy instead of the usual two. The missing part includes two DNA markers, RP11-260K8 and RP11-479F13

Is there a 2p deletion syndrome?

There is no single syndrome that affects everyone with a piece missing from 2p. There is a syndrome that affects people with a microdeletion at 2p15p16.1:

Unique publishes a separate guide to 2p15p16.1 microdeletions

Since this guide was first written, other syndromes have emerged:

Unique now publishes separate guides to 2p16.3 (NRXN1) deletions, Sox11 syndrome and 2p25.2 deletions and MYT1L syndrome and 2p25.3 deletions

Are there people with a 2p deletion who are healthy, have no major medical problems or birth anomalies and have developed typically?

Yes. There is one early description in the medical literature of a family whose development was unaffected by their unusual chromosomes – in their case, the deletion covered the bands 2p12.2 to 2p13 (Lambert 1991).



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2p11.2p13 Deletions:

Ten people have been reported or described to Unique. Two children have been described with a microdeletion at 2p11.2 and an adult with a small deletion at 2p12.2p13 (Voullaire 1989; Lambert 1991; Prasher 1993; Los 1994; Wenger 1997; Lacbawan 1999; Unique).

Will there be any clinical sign in the pregnancy that the baby has a chromosome disorder?
Not necessarily, although one baby was growing slowly by the third trimester (Los 1994).

How might the baby be at birth?

There's quite a variety. Babies have generally been born within a week or two of their due date, some after an uneventful delivery. One mother went 16 days beyond her due date and had a very long labour ending in a vacuum extraction; her baby had good Apgar scores (a 0-10 scale of wellbeing) of 7 at 1 minute and 9 at 5 minutes after birth, only losing a point for low muscle tone. Another mother had an emergency Caesarean after the placenta came away from the wall of the uterus. Out of seven babies, four were a good weight (3.4-4kg; 7lb 8oz-8lb 13oz) but three were unexpectedly small, weighing around 2.5kg (5lb 8oz). Three babies needed extra oxygen to help with their breathing and another baby needed extra care because he couldn't maintain his body temperature. Generally, babies only needed a few days in hospital before going home. One baby was born with a weakness on one side of the diaphragm that keeps the contents of the abdomen separate from the chest and this displaced his heart.

What about food and eating?

It is quite likely that a baby will have difficulties in the early days with both sucking and swallowing and you may find that your baby feeds very slowly. Breast feeding may prove too much of a struggle and your baby may do better on breast milk given from a bottle, formula or enriched formula. If feeding is very effortful, your baby may be helped by being fed through a soft, fine tube threaded through the nose. It is still possible to give breast milk by tube, but some babies may also need high-energy top-up feeds to maintain their growth rate.

An unusually high palate is common in babies and children with a 2p deletion. A high palate can make latching on and sucking more difficult and some babies make better progress with a nipple shield or, if bottle fed, with a variable-flow teat or one specially adapted for premature babies. After weaning, solids may become lodged in the palate; regular sips of drink can help to prevent this.

Some babies also experience reflux, in which feeds and stomach contents return up the food passage (oesophagus) and may be vomited or inhaled, causing chest infections known as aspiration pneumonia. Careful feeding and positioning both for feeds and sleeping, the use of feed thickeners and medications prescribed to inhibit gastric acid may control reflux. If these measures are not enough, an operation called a fundoplication can be performed to improve the function of the valve from the stomach to the food passage.

Weaning, drinking from a cup and self-feeding are likely to be delayed and some babies may not tolerate thickened and solid foods until their second year while others only take very small volumes of food. Children may have particular difficulty in chewing and remain at risk of choking and so need supervision while eating or feeding themselves.

Constipation was seen in four children and is generally quite common in children with a chromosome disorder but usually responds to increased fluid, fibre, or prescribed medication.

If she had not been my first baby, I would have known something was wrong the first time I nursed her. As a newborn she had a very weak suck and had difficulty coordinating sucking and swallowing. She choked and gasped frequently and fell asleep before getting enough milk. Breast feeding was very difficult and she did not thrive, so she switched to formula milk at around 10 weeks. She gained weight then but still had trouble with the nipple, there was still a lot of gasping and choking."

Will my baby or child look different?

You may notice that your baby has certain unusual facial features and that he or she looks any pictures of children with a 2p deletion in this leaflet. Many babies, although not all, have a rectangular, narrow face with a wide bridge across the nose and eyes spaced wide apart. Their chin and lower jaw may be small and their ears set low on the side of the head and perhaps unusually shaped. Other babies may have further distinctive facial features. As a rule, these features are quite subtle and have no effect on a baby's health or wellbeing, although a very small jaw may make sucking at the breast harder.

Hands and feet

In many babies and children, the hands and/or the feet have at least some unusual features. For example, the fingers may be long and slender, although the tips may be short. Some fingers – especially the little finger – may curve inwards and they may be bent in a semi-fixed position, so they do not move freely at the joints. When they move, the fingers may overlap. The fifth fingers may be short; the thumbs may be held in a clasped position.

The feet may be long and perhaps narrow and some of the toes may overlap; the big toe may not be the longest on the foot and may be turned inwards. The heels may stick out. One child has flat feet and tight heel cords, needing regular stretching at physiotherapy.

Two babies were born with talipes, where one foot or both is held at an unusual angle and treatment is needed to straighten the foot so that it can grow and develop usually. First-line treatment is non-surgical and may include manipulation, casting, taping, physiotherapy, and splinting, followed by bracing to prevent relapse. Surgery and sometimes splinting are considered if non-surgical treatments are not completely successful. The foot position may relapse as the child grows and develops, making more surgery necessary.

Is there a typical growth pattern?

There is quite limited information on growth, but it seems that babies who are small at birth may continue to grow slowly and become short children and adults. Babies who are larger and longer at birth seem more likely to continue to grow at an expected pace during childhood. Body build varies a lot, with some children very thin while others are sturdy. Low muscle tone in the abdomen can make children's stomach stick out.

Development

Babies and children are very likely to 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.

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

Children with a 2p11.2p13 deletion can be expected to need some support with their learning, but the amount of support needed can't be predicted just from the karyotype. There are children with a 2p deletion who attend mainstream (regular) schools with appropriate support and others, probably the majority, whose needs are better met in an environment that caters for their special needs.

As a broad generalisation, most children known to Unique are working at the level of a child around half their age. While they may well acquire some reading and writing skills, the emphasis in their education is likely to be on acquiring skills for living. Writing is likely to be especially slow to develop in children with low muscle tone in the hands and they may progress faster using a touch screen or keyboard.

> ***She has a very good visual memory and is very determined. She can read and write her own name with letter order prompts and draws faces, human forms, and many shapes. She enjoys watching videos, riding her bike, looking at books, organising long lines of hot wheels cars and toy plastic animals and playing outdoors" - 10 years***

How might communication be affected?

Children will generally experience some delay in understanding and expressing themselves in speech. Progress is slowed overall, with first words emerging late and some but not all children acquiring more complex speech patterns. Children who do not use speech can communicate their needs with gestures, facial expression, objects of reference or pictures or using sign language or communication devices.

In general, it appears that the use of language reflects children's learning ability and those children who face the greatest learning challenges are least likely to speak or to use more than the occasional word. Two children with relatively fluent language both have smaller deletions, but we can't be certain that the main influence on speech is the size of the deletion.

Sitting, moving gross motor skills

The major baby milestones of gaining head control, rolling over, sitting, becoming mobile, and walking are very likely to be delayed. This means that early physiotherapy (physical therapy) and stimulation programmes should be made available to all children with a 2p deletion at the very least as a precautionary measure.

There is a quite broad range of ages at which children gain control of their bodies and become mobile. Unique's records show that babies first rolled over between three and nine months; they sat alone between seven months and 2½ years; they became mobile by scooting, rolling, bottom-shuffling or crawling between their first and second birthday; and they started to walk alone between 17 months and 3½ years. Once on their feet, some children's walk may remain stiff and clumsy, especially on uneven ground and they may need rails to help when climbing steps or stairs. Others progress quickly to running and skipping.

Many babies have a degree of low muscle tone (hypotonia, causing floppiness), but muscle tone may also be raised (hypertonia), and some children have variable tone in different parts of the body. Treatment for hypertonia can include range of motion exercises, stretching and physiotherapy to prevent joints from contracting. Surgery for tendon release may be undertaken in some cases. Medications that relieve spasticity may also be considered.

Any anomalies of the angle of the foot, such as club foot (talipes) have an obvious impact on mobility but once corrected by surgery or physiotherapy, a smooth walking style should become possible.

Development: hand use and coordination (fine motor skills) and self-care

Most children experience considerable delay in controlling their hand use. Recurring themes in parental reports are a delayed pincer grasp in babies, weak hand grip, and a delay in holding objects. Young children find manipulating small objects such as buttons, poppers and zippers a challenge but with consistent training and verbal prompting many achieve feeding and dressing skills by mid childhood. In terms of self-care, most youngsters achieve a quite high level of collaborative independence in dressing, washing, and personal care tasks. It may not be appropriate for parents to expect toileting to occur at the same age as other unaffected children.

> ***Despite very low muscle tone in her hands and fingers, she can write her name with reminders about the order of letters, colour beautifully within lines and can trace other numbers and letters very well. She can also cut with scissors, though not perfectly. She cannot zip or button yet, tie her shoes or put them on or take them off but she can pull pants up and down with help. She can brush her teeth but for hygiene reasons has it done for her. She is now potty-trained and wears pull-ups as she is dry most of day." - 10 years***

Behaviour

Unique has fairly detailed information on the behaviour of four children with a 2p11.2p13 deletion. There is also a brief description of an adult in the medical literature (Prasher 1993; Unique). This is too small a number for a definitive picture to emerge but the remarks that follow may give families helpful insights.

Families most frequently mention that their children are happy and lively and have good social interactions, although their behaviour may be typical of a child much younger than their actual age and they may choose to play with younger children rather than with their peers. A baby was described as crying a lot and being 'hard to reach.' Among older children, frustration at being unable to do what they want can lead to challenging behaviour and children then benefit from set boundaries and constructive support in building friendships with other children.

The report in the medical literature describes a very different child who was put into a home at birth and went on to show long-lasting behaviour difficulties with aggression and petty criminal behaviour.

> ***Her behaviour is getting better as she understands more speech, especially the concept of time and waiting." - 10 years***

Happy and healthy?

There is no evidence that children with this deletion will be any more unwell than children without a chromosome disorder. Like other young children, they have repeated coughs and colds and are prone to develop ear and respiratory infections. However, with their precarious weight gain, some young children may be more likely to stop feeding and lose more weight while ill than other children and to need to spend time in hospital recovering (Unique). By the age of 9 or 10, families report that their children are happy and healthy.

Medical concerns



Children with a 2p11.2p13 deletion are mostly healthy (see above). But the medical concerns that follow have been found in more than one child; they are listed in order of frequency. Most of the concerns are fairly common among children with a chromosome disorder and it is not yet known whether they are typical or not for those with a specific deletion within 2p11.2p13.

Eyesight

A problem with eyesight has been found in six children. With a 2p11.2p13 Problems are mostly easily correctable with glasses (short sight) deletion or with patching, exercises, or surgical correction (squint, strabismus). One child had mild nystagmus (the eyes rove back and forth), and another child had a developmental defect of the iris known as a coloboma but has perfect vision (Prasher 1993; Los 1994; Wenger 1997; Unique).

Minor genital anomalies

Minor genital anomalies such as testicles that have not descended into the scrotum by the time of birth are fairly common in the general population and somewhat more common among babies with a chromosome disorder. Three baby boys out of eight were born with undescended testicles and one also had a very small penis and hypospadias, where the hole usually situated at the end is on the underside instead. Treatment for undescended testicles is usually needed if the testicles do not descend naturally in time. The testicles can be brought down in a short operation under general anaesthetic called an orchidopexy. Very mild hypospadias may need no treatment but otherwise it can be corrected surgically. An opening for the urethra is created at the tip of the penis which is straightened if necessary. As the foreskin may be used during surgery, boys with hypospadias are not circumcised (Los 1994; Wenger 1997; Unique).

Seizures

Seizures may be more common in this group of children than has been suspected. Although none of the children described in the medical literature have had seizures, four of Unique's eight members with a deletion in the 2p11.2p13 region have. One child with a microdeletion at 2p11.2 was affected. One child had no more than two febrile seizures as a toddler, but the others developed a seizure disorder and in two it was characterised as severe. Seizures are generally well controlled with anti-epileptic medication, but one child was due to be fitted with a vagus nerve stimulator to improve control (Unique).

Heart

The great majority of babies have been born with a healthy heart and have not developed problems later. One baby had a slight murmur, which resolved naturally; another had a suspected small hole between the lower pumping chambers of the heart (ventricular septal defect/ VSD). A small VSD may well heal naturally; a larger VSD usually needs surgical repair to prevent lung problems that would develop from exposure to extra blood flow. This baby's heart was displaced by a fault in the muscular barrier between the chest and abdomen that allowed some abdominal contents to bulge upwards (dextrocardia due to diaphragm eventration) (Wenger 1997; Unique).

Other medical concerns

Most babies and children were otherwise healthy. When a problem affects just one child in a group as small as this, it isn't at all certain that the chromosome deletion is the cause. Features that affected just one child are: a tethered cord (the usually mobile and free spinal cord is held in one place; treatment is surgical - a neurosurgeon will free the tissue that is preventing the spinal cord from moving within the spine); horseshoe kidneys (the bottom points of the two usually separate kidneys are joined, creating a horseshoe shape, in itself not harmful and some children have no symptoms and may need no treatment. However, a horseshoe kidney can increase the risk of urinary tract infections. Around one third of people with horseshoe kidney have another anomaly or complication which may need supportive treatment); eventration of the diaphragm (see Heart); choanal stenosis (a blockage in the nasal passages needing surgical correction); vitiligo developing at two years of age (patches of whitish skin caused by loss of the pigment-making cells in the skin); and a permanent hearing loss (Los 1994; Wenger 1997; Lacbawan 1999; Unique).

2p16p21/22 deletions

Twenty people have been reported in the medical literature or described to Unique, three of them adults. Four have a large deletion of most of 2p16 to 2p21/2 (Sanders 2003; Lucci-Cordisco 2004; Unique). Two children have a microdeletion at 2p16.3 (Krepischi-Santos 2006; Zahir 2008). Fourteen people have been described with a deletion between 2p21 and 2p23, 10 of them with mild or more serious holoprosencephaly (HPE, see page 21) (Münke 1988; Grundy 1989; Wilson 1989; Sawyer 1994; Schell 1996). A child with a deletion of 2p22 and three individuals with a 2p21p22.2 deletion had no evidence of this brain disorder (Webb 1987; Armstrong 2006; Unique). These four are included.

Will there be clinical signs in the pregnancy of the chromosome disorder?

Apart from a baby with HPE, it is unlikely. Pregnancy is usually typical throughout, and babies are born at or around their due date, although one baby was born at 29 weeks after his mother had a urinary infection (Unique).

How might the baby be at birth?

Babies born at term have been a good size and weight at birth and have generally been healthy. One baby had low Apgar scores of 4 at one minute and 8 at 10 minutes. The Apgar score is a measure of wellbeing in a new baby on a scale of 0-10. This baby spent a week in special care and had early difficulties with feeding. Another baby was floppy and had the digestive disorder Hirschsprung's disease. The premature baby needed help with his breathing for 12 months (Webb 1987; Unique).

Will my baby or child look different?

You may notice that your baby has certain unusual facial features and that he or she looks a little like others with a 2p deletion in this leaflet. Any unusual features are typically subtle. Features noted in individual babies include a small, asymmetrically shaped head; prominent or narrow forehead; large eyes that may be close together and have skinfolds across the inner corners; a nose with a prominent bridge or small nostrils; an unusually short or long groove between the nose and upper lip; somewhat unformed ears; and either an unusually hairy aspect or receding hair from the temples (Webb 1987; Sanders 2003; Lucci-Cordisco 2004; Armstrong 2006; Zahir 2008; Unique).

Hands and feet

In some babies and children, the hands and/or the feet have some unusual features. For example, the fingers and one or more toes may be short. Some fingers and toes may be bridged by skin and some of the finger joints may be unusually bendy. A Unique family remarked on their son's long arms (Lucci-Cordisco 2004; Zahir 2008; Unique)

Is there a typical growth pattern?

Probably not. From a good size and weight at birth, some babies grow at an expected rate and become average-sized children; others grow tall and heavy; one adult, however, was in the smallest three per cent of the population for height, though she was relatively heavy for her height (Sanders 2003; Lucci-Cordisco 2004; Zahir 2008; Unique).

Development

Babies and children are likely to show some developmental delay although this may not be obvious at first. Early intervention with stimulation and play schemes will help. The extent of any delay varies a lot, and it is better to let your child show his own pace of development. You can turn to your children's centre, developmental paediatrician, opportunity playgroup, portage scheme, or health visitor for ideas on suitable stimulation.

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

Children with a 2p16p22 deletion can be expected to need some support with their learning but the amount of support needed can't be predicted just from the karyotype.

There are reports of children and an adult with a 2p deletion with a wide range of learning difficulties – from barely noticeable to severe. Significant numbers attend mainstream (regular) schools, with some extra support. A child who was assessed as having overall mild difficulties with learning was in the borderline category at 5 years old for understanding words and processing information. Two years later, he had problems with problem solving, difficulty organising and sequencing tasks and suffered from mental fatigue. By the time he was nine, his IQ was assessed at 90 on verbal scores and 70 for performance. A young adult assessed as having overall severe difficulties is not reading or writing but looks at pictures and holds a pencil with encouragement. He has a good memory for places he wants to go to. He enjoys going to football matches with his father and loves watching sport on TV and taking part according to his abilities. He also loves pop music.

How might communication be affected?

Children will generally experience some delay in understanding and expressing themselves in speech. Progress is slowed overall, with first words emerging late – around 3 years - and some but not all children acquiring more complex speech patterns. Children who do not use speech can communicate their needs with gestures, facial expression, objects of reference or pictures or using sign language or communication devices.

> ***If he's thirsty, he will fetch a drink or bottle."***

Sitting, moving: gross motor skills

The major baby milestones of gaining head control, rolling over, sitting, becoming mobile, and walking are likely to be somewhat delayed but in this group the delay seems to be quite small, with toddlers starting to walk between 17 and 20 months. Once on their feet, the evidence from Unique is that children progress steadily. One young adult enjoys trampolining, horse riding, walks, and bowling.

One child with a microdeletion at 2p16.3 showed a tendency to exaggeratedly bendy joints, which easily became dislocated, suggesting the possibility of connective tissue disease (Krepischi-Santos 2006).

> ***His mobility is good and he climbs stairs well although he doesn't like coming down and has to be watched. He is rather clumsy and trips regularly. We use a wheelchair for long distances as he doesn't always want to walk and can drop to the floor."***

Development: hand use and coordination (fine motor skills) and self-care

Most children experience delay in controlling their hand use. Recurring themes in parental reports are a delayed pincer grasp in babies, weak hand grip, and a delay in holding objects. Young children find manipulating small objects such as buttons, poppers and zippers a challenge but with consistent training and verbal prompting many achieve feeding and dressing skills.

As for self-care, most youngsters achieve a quite high level of collaborative independence in dressing, washing, and personal care tasks. Toileting is also likely to be late.

> ***He needs help to dress, bath and shave. His co-ordination is still poor and though he uses a spoon or fork to eat he is very messy. His hands are quite shaky - too shaky to put a key into a lock - possibly due to his epilepsy medication."***

Behaviour

There is fairly detailed information on the behaviour of one child and two adults with a 2p16p22 deletion. (Lucci-Cordisco 2004; Zahir 2008; Unique). This is not enough for a definitive picture but the remarks that follow may give families helpful insights.

A 37-year-old adult is described as having 'good family and social interactions'. A 20year-old adult is also described as 'a lovely boy, happy and content with simple things'. Adolescence brought behaviour changes explained by frustration or his inability to communicate but he remained very loving, undemanding, and happy if his known routine was followed. He was sociable and confident enough to take a hand and dance at a disco.

The child developed some behaviour difficulties from the age of eight, for example inappropriate social behaviour, inability to accept criticism, temper difficulties, argumentativeness and odd fears, ways of relating and preoccupations. By nine he had a tendency to live in his own world and had developed fixed interests as well as difficulty with his routine being disturbed and certain behaviours reminiscent of autism such as missing social cues, lining up objects and ritualistic activities. Although he scored above average on scales for autism and Asperger's syndrome, he scored too low for diagnosis.

> ***Happy with simple things like playing football, videos, ice cream, or food."***

Medical concerns

Children with a 2p16p22 deletion are mostly healthy, although one boy had long-term consequences of prematurity (Unique). There is no evidence of hearing loss or dental problems and only one child has an eye problem (nystagmus, wobbly eyes) (Unique). Apart from those with HPE (page 21) and two boys with undescended testicles (Grundy 1989; Unique), the medical concerns that follow have been found in one child or adult only and it is not yet known whether or not they are typical for those with a specific deletion within 2p16p22. One child developed epilepsy as a toddler but the seizures were well controlled during adulthood; a baby was born with the digestive disorder Hirschsprung's disease; another was born with a small hole between the upper holding chambers of the heart (atrial septal defect/ASD); another child had five vertebrae joined together, as well as an extra rib; he also had asthma attacks severe enough to need hospital treatment and urinary tract infections that continued until he was circumcised at the age of 11. An adenoma (cancer of glandular tissue) was successfully removed from the colon of an adult aged 37 years (Webb 1987; Sanders 2003; Lucci-Cordisco 2004; Krepischi-Santos 2006; Zahir 2008; Unique).

2p distal deletions

"He is an absolute joy. Even with all of his challenges I couldn't imagine life without him. At the time I received his diagnosis, I would never have thought this experience would be so positive."

"Even with his seizures, surgery, and the uncertainty, we laugh more than most families. Every day is a gift."

Fourteen children have been reported in the medical literature or described to Unique.
The size of the deletion varies considerably between individuals (Zackai 1977; Emanuel 1979; Neidich 1987; Penchaszadeh 1987; Francis 1990; Saal 1996; Brondum-Nielsen 2005; Ravnan 2006; Lo-Castro 2008; Unique).

Will there be any clinical sign in the pregnancy that the baby has a chromosome disorder?

There may be. In two cases, early serum screening tests came back with unusual results. One mother had no detectable alpha fetoprotein (the test used to screen for spina bifida); another indicated a raised risk of a chromosome disorder. This baby and one other were consistently small throughout pregnancy (Penchaszdeh 1987; Unique).

How might the baby be at birth?

There's quite a lot of variation. Babies have generally been born within a week or two of their due date, some after an uneventful delivery. Three babies were delivered early, two by Caesarean section, after concern over their condition. Two babies were born prematurely, one at 34 and one at 36 weeks. Out of eight babies born at or near their due date, four were a good weight (3-3.9 kg; 6lb 10oz - 8lb 10oz) but four were unexpectedly small, weighing 2-2.5kg (4lb 7oz - 5lb 8oz). Two babies needed help with their breathing; both had a structural anomaly of the breathing passages – one the combination of a cleft palate (split in the roof of the mouth) and an unusually small jaw known as the Pierre Robin sequence, the other a marked narrowing of the food passage together with a channel linking the windpipe to the food passage. Two further babies needed treatment for high levels of bilirubin (jaundice) in hospital before going home (Neidich 1987; Penchaszdeh 1987; Francis 1990; Saal 1996; Brondum-Nielsen 2005; Unique).

What about food and eating?

It is very likely that a baby will have difficulties in the early days with sucking, swallowing, and coordinating the two and you may find that your baby feeds too slowly and in too small quantities to satisfy his own nutritional needs. Breast feeding may prove too much of a struggle and your baby may do better on breast milk given from a bottle, or on formula or enriched formula. If feeding is very effortful, your baby may be helped by being fed through a soft, fine tube threaded through the nose. It is still possible to give breast milk by tube, but some babies may also need high-energy top-up feeds to maintain their growth rate. Babies born with additional difficulties such as a cleft palate will need specialist support and may occasionally benefit from feeding direct into the stomach through a gastrostomy tube.

An unusually high palate can occur in babies and children with a 2p distal deletion. A high palate can make latching on and sucking more difficult and some babies make better progress with a nipple shield or, if bottle fed, with a variable-flow teat or one specially adapted for premature babies. After weaning, solids may become lodged in the palate; regular sips of drink can help to prevent this.

Some babies also experience reflux, in which feeds and stomach contents return up the food passage (oesophagus) and may be vomited or inhaled, causing chest infections known as aspiration pneumonia.

Careful feeding and positioning both for feeds and sleeping, the use of feed thickeners and medications prescribed to inhibit gastric acid may control reflux. If these measures are not enough, an operation called a fundoplication can be performed to improve the function of the valve from the stomach to the food passage.

Weaning, drinking from a cup and self-feeding are likely to be delayed and some babies will not tolerate thickened and solid foods until late while others only take very small volumes of food. Children may have particular difficulty in chewing and remain at risk of choking and so need supervision while eating or feeding themselves.

Will my baby or child look different?

You may notice that your baby has certain unusual facial features. Typically, babies and children have a very small head. Listed in order of frequency, other features noted in the medical literature and at Unique are: a remarkably small lower jaw and chin; ears set below the eye line; a narrow, rectangular face; a visible or palpable ridge down the middle of the forehead (metopic suture); the back of the head sticks out; small eyes; arched eyebrows that may meet in the middle; hooded or drooping upper eyelids; tiny skinfolds across the inner corner of the eyes; a prominent, possibly high forehead; a small nose; a low nasal bridge; and asymmetry between the two sides of the face.

As a rule, these features are quite subtle and have no effect on a baby's health or wellbeing, although a very small jaw may make sucking at the breast harder and hooded eyelids may need lifting if they interfere with vision (Zackai 1977; Emanuel 1979; Neidich 1987; Penchaszdeh 1987; Francis 1990; Saal 1996; Brondum-Nielsen 2005; LoCastro 2008; Unique).

"A very adorable face."

Hands and feet

In many babies and children, the hands and/or the feet have at least some unusual features. For example, the hands are typically (very) small and the fingers are short. Some fingers – especially the little finger – may curve inwards and have a single crease. Some fingers may be bent in a semi-fixed position, so they do not move freely at the joints. There may be a single continuous crease across the palm of the hand, and both finger and toenails may be very thin and brittle, so they never need trimming.

The feet may be small and the toes short; toes – especially the second and third – may be joined by a bridge of skin. There may be a wide 'sandal' gap between the big toe and its neighbour, and the heels may stick out. One child has 'banana feet' (metatarsus adductus), an unusual position where the front part of the foot turns inwards.

By and large, these features will not affect the way a child walks, although a child with banana feet will usually need physiotherapy to help straighten them ready for walking.

Is there a typical growth pattern?

Regardless of size and length at birth, it seems that babies grow slowly - sometimes very slowly - and become short children. The exception are those babies with the tiniest deletions within the subtelomere portion of chromosome 2p, where there is some evidence that growth and eventual height may be closer to average. Body build can vary, but there are repeated reports of children being very thin as well as small.

Development

Babies and children are very likely to 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.

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

Children with a distal 2p deletion can be expected to need some support with their learning but the amount of support needed can't be predicted just from the karyotype. The overall picture suggests that children will have a moderate to severe level of learning difficulty and will benefit most from being educated in an environment that caters for their individual special needs, whether that is in a mainstream (regular), special or home setting. While children may well acquire some recognition and literacy skills, the emphasis in their education is likely to be on acquiring skills for living.

> ***His strengths are music, his personality, and his sense of humour. He remembers signs, places and people's names and is determined, well-motivated and open to learning." - 2 years***

"He has some basic computer skills and remembers signs and music relatively well. He has a great sense of humour and uses it in his learning." - 9 years

How might communication be affected?

Children will generally experience some delay in understanding and expressing themselves using spoken language. Progress is slowed overall, with first words emerging late, between two and seven years and possibly even later, if at all. Children who do not use speech may well have good underlying communication skills and communicate their needs with gestures, facial expression, objects of reference or pictures or using sign language or communication devices.

In general, it appears that the use of language reflects children's learning ability and those children who face the greatest learning challenges are least likely to speak. Children with low muscle tone in the mouth and face will also have difficulty making the sounds of speech. It is important to have early access to speech therapy (Francis 1990; Saal 1996; Lo-Castro 2008; Unique).

"He signs, pushes, pulls and uses gestures and vocal noises. So far, he has no words but babbles and understands more than he can express." - 2 years

"He can say several vowels and a few consonants, has several words, signs, gestures and uses a computer communication device. He understands much more than he can express." - 9 years

Sitting, moving gross motor skills

The major baby milestones of gaining head control, rolling over, sitting, becoming mobile, and walking are very likely to be delayed. This means that early physiotherapy
(physical therapy) and stimulation programmes should be made available to all children with a distal 2p deletion.



There is a quite broad range of ages at which children gain control of their bodies and become mobile. Unique's records and the medical literature show that babies first rolled over between four and 12 months; they sat alone between six and 17 months; they became mobile by scooting, rolling, bottom-shuffling, commando crawling or crawling between their first and second birthday; and they started to walk alone between 12 months and six years, sometimes after a period with a stander or walker. Once on their feet, some children's walk may remain clumsy especially on uneven ground, they may have difficulties with balance or may tire easily and may need rails to help when climbing steps or stairs.

Many babies have a degree of low muscle tone (hypotonia, causing floppiness) and benefit from early intervention with physiotherapy (physical therapy) as well as supportive clothing and devices such as ankle and leg orthoses. In some children, the low muscle tone improves with age while in others it persists, making everyday movements such as walking and standing effortful (Neidich 1987; Penchaszdeh 1987; Francis 1990; Saal 1996; Lo-Castro 2008; Unique).

Development: hand use and coordination (fine motor skills) and self-care

Most children experience considerable delay in controlling their hand use. Recurring themes in parental reports are a delayed pincer grasp in babies, a weak hand grip, a tremor, and a delay in holding objects and passing them from hand to hand. Young children find manipulating small objects such as buttons, poppers and zippers a challenge but with consistent training and verbal prompting many achieve feeding and dressing skills by mid childhood.

In terms of self-care, even very young children can achieve a quite high level of collaborative independence in dressing, washing, and personal care tasks. It may not be appropriate for parents to expect toileting to occur at the same age as other unaffected children and the evidence from Unique suggests that successful toilet training starts from around five years.

> ***He is behind his peers but continues to progress steadily. He can brush his teeth with help and helps with dressing. He can't do it himself but knows what to do." - 2 years***

"He can brush his teeth and remove his foot braces with very little help. He can use a potty but does not tell before he needs to go, so he wears diapers. He's learning to pull up his pants." - 9 years

Behaviour

Unique has brief descriptions of the behaviour of six babies or children with a distal 2p deletion. There is also a brief description of a child in the medical literature (Lo-Castro 2008; Unique). This is too small a number for a definitive picture to emerge but the remarks that follow may give families helpful insights. Families most frequently mention that their babies are happy and lively and have good social interactions, although their behaviour may be typical of a child younger than their actual age and they may choose to play with younger children. The report in the medical literature describes a child who was met the criteria for a diagnosis of autism and was also hyperactive.

Happy and healthy?

While some young babies and children with a distal 2p deletion have good general health, there is some evidence that others will have an increased number of coughs and colds in their early years and develop more ear and respiratory infections than other children. In particular, with their precarious weight gain, some children are more likely to stop feeding and lose more weight while ill than other children and to need to spend time in hospital recovering. One child had multiple other health problems and suffered from pneumonia (Unique).

Medical concerns

Seizures

Seizures are fairly common in this group of children, starting in babyhood or early childhood. Three of Unique's six members have had seizures, in one child associated mainly with fevers. This child was able to come off anti-epileptic medication with no return of seizures after four years by the age of five; another child's family was considering vagus nerve stimulation as medication was not controlling daily seizure activity. Children reported in the medical literature were well controlled on antiepileptic medication (Neidich 1987; Penchaszdeh 1987; Francis 1990; Unique).

Minor genital anomalies

Minor genital anomalies such as testicles that have not descended into the scrotum by the time of birth are fairly common in the general population and somewhat more common among babies with a chromosome disorder. One baby boy was born with undescended testicles and two had a very small penis. Treatment for undescended testicles is usually needed if the testicles do not descend naturally in time. The testicles can be brought down in a short operation under general anaesthetic (Zackai 1977; Unique).

Eyesight

A problem with eyesight has been found in five children. Problems are mostly easily correctable with glasses (long sight) or with patching, exercises, or surgical correction (squint, strabismus). One child had nystagmus (the eyes rove back and forth) and unusually small corneas (the transparent disc-like front part of the eye) while another child had an unusually small right eye and a missing optic nerve on that side (Emanuel 1979; Penchaszdeh 1987; Lo-Castro 2008; Unique).

Hearing

Most children have had good hearing. A problem has been identified in four children, ranging from a possible slight hearing loss to a severe loss in one ear and a moderate loss in the other. Where a hearing impairment is caused by a build-up of fluid behind the eardrum, tiny plastic tubes can be inserted to equalise the air pressure and resolve the problem. Where the hearing loss is more severe and permanent, hearing aids may be needed (Francis 1990; Saal 1996; Unique).

Spine

Three children have been found to have a curvature of the spine. In many children a slight curve will correct itself in time, but progressive scoliosis can lead to problems sitting and if it is severe can cause heart and lung problems. Treatment depends on the severity and progression of the curve but may involve wearing a body brace and surgery to fuse the vertebrae. In one child one of the vertebrae in the spine slipped forward out of alignment with the vertebra below it. This condition is known as spondylolisthesis and usually responds well for a time to rest, pain relief, bracing, or physiotherapy. For a permanent solution, correction may be needed by spinal fusion (Lo-Castro 2008; Unique).

Heart

The great majority of babies, including Unique members, have been born with a healthy heart and have not developed problems later. One baby had small holes between the upper and the lower pumping chambers of the heart (atrial septal defect/ ASD; ventricular septal defect/ VSD); another had a moderate sized VSD. Small septal defects may well heal naturally; larger ones usually need surgical repair (Penchaszdeh 1987; Brondum-Nielsen 2005).

Brain: hydrocephalus

Among babies and children who have had imaging of the head and brain, two have had an increase in the cerebro-spinal fluid within the fluid-filled spaces in the brain, in one case enough to need a drain (shunt) inserted. A search for a cause for the hydrocephalus in one child revealed a small choroid plexus cyst. This is a fluid-filled area in the gland that makes the fluid that circulates round the brain. It also revealed a pineal cyst (usually an incidental and harmless finding) (Unique).

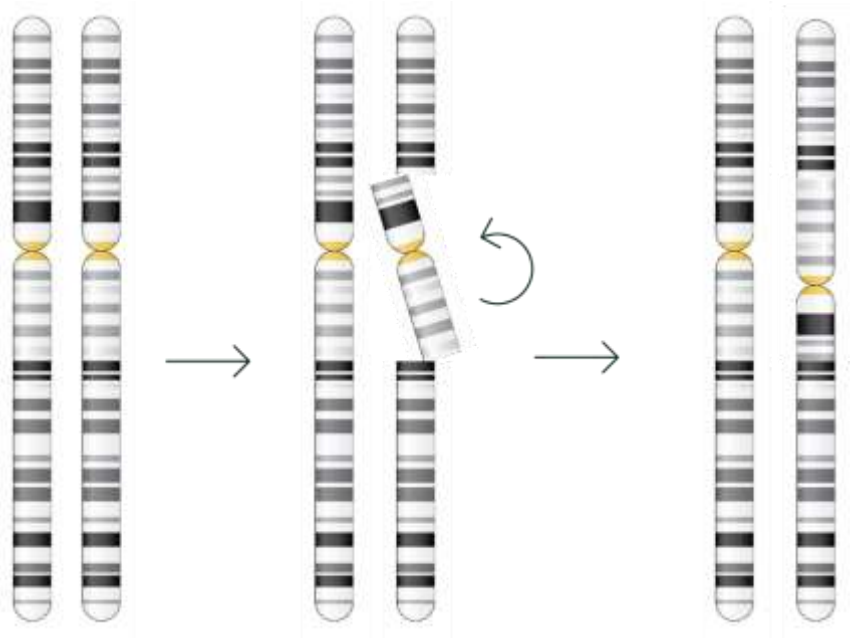
Other medical concerns

Most babies and children were otherwise healthy. When a problem affects just one child in a group as small as this, it isn't at all certain that the chromosome deletion is the cause. Problems that affected just one child are: a narrowing of part of the intestines known as the duodenum together with a condition known as Meckel's diverticulum (where a small pouch is left in the wall of the intestine near the junction of the small and large intestine as a remnant of tissue from life before birth. Most people do not have any symptoms or problems but in some cases the tissue produces acid. The intestine can also become blocked by Meckel's diverticulum. If symptoms develop, the diverticulum can be removed with a surgical operation. After surgery children usually thrive with no long-term gastrointestinal problems; a diaphragmatic hernia (a hole in the muscular wall separating the heart and lungs from the contents of the abdomen. The bowel, stomach or liver take up part of the space in the chest, potentially depriving the lungs and heart of room to develop properly. Once a baby's condition has been stabilised the hernia will be repaired and support given for breathing for as long as the baby needs it); seasonal allergies; and radioulnar synostosis (the two bones in the forearm are fused towards the wrist, so it is impossible to rotate the arm and elbow movements may be limited) (Neidich 1987; Brondum-Nielsen 2005; Unique).

How did the 2p deletion occur?

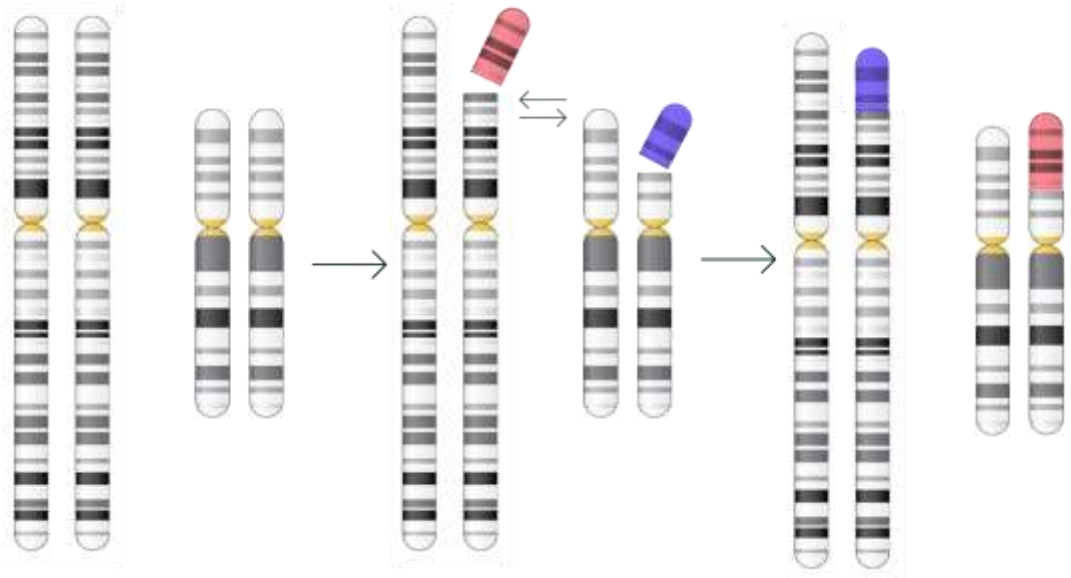
A 2p deletion can arise in a number of different ways. It can be inherited or not inherited, so a blood test to check both parents' chromosomes is needed first. If the blood test shows conclusively that both parents have usual chromosomes, the deletion has almost certainly not been inherited but has occurred as a new event, called **de novo** (dn), meaning 'new.' De novo 2p deletions are caused by a sporadic mistake that is thought to occur when the parents' sperm or egg cells are formed or very soon after conception (see page 2).

In the general population, around one person in 12,000 has an unusual arrangement of chromosome 2 that causes them no problems but may possibly make it more likely that they may have a pregnancy with a proximal 2p deletion. In this arrangement, a section of chromosome 2 has broken off, swivelled round 180 degrees, and reinserted itself into the chromosome. This means that all the chromosome material and genes are present, but in the rearranged section they run in the opposite direction to the rest of the chromosome arm. This arrangement is known as a **pericentric inversion**. In a karyotype, it will look like this: inv (2) (p11.2q13). Problems are so unusual that it isn't thought necessary for people with this inversion to have prenatal diagnosis, but it's been suggested that their children should be monitored in case they have a related deletion (Jacobs 1974; Lacbawan 1999).



This inversion is usually a benign family variant

In some couples, one parent is found to have a balanced rearrangement of their own chromosomes. This is usually a rearrangement known as a balanced translocation in which chromosome material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. When a parent has this type of balanced translocation, there is a risk that their children will have not only the 2p deletion, but also extra material from the other chromosome involved in the swap.

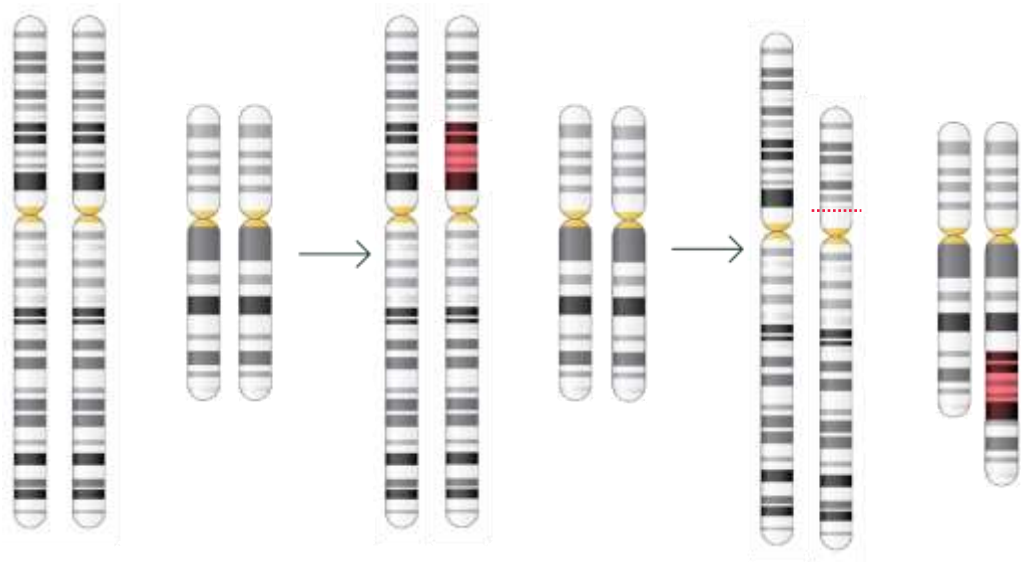


A balanced translocation between the short arms of chromosomes 2 and 16

Insertion

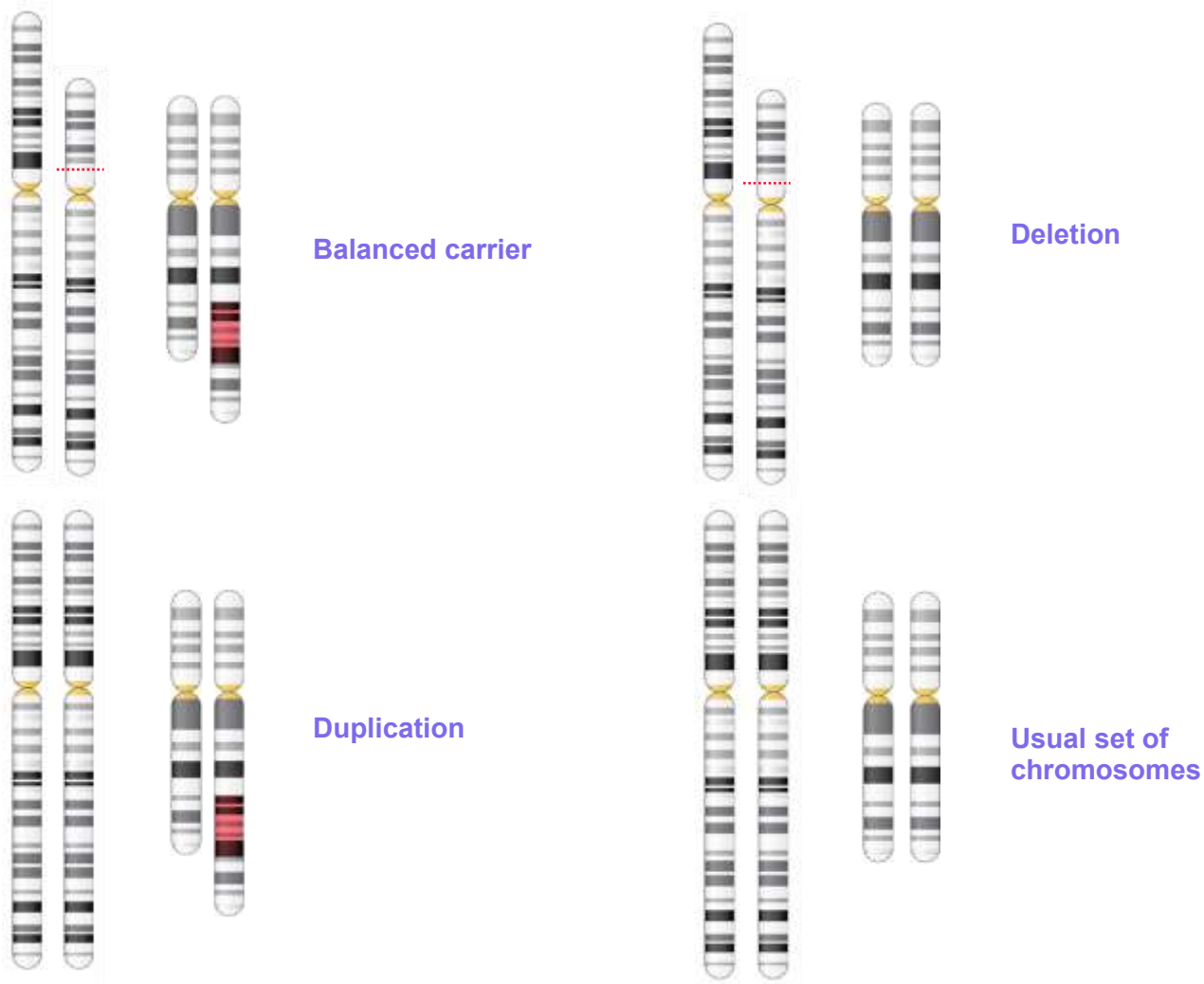
An insertion is another type of translocation. It can be de novo or inherited from a parent with a balanced insertional translocation (see diagram below). Insertional translocations are rare chromosomal rearrangements found in only one in 80,000 newborn babies (Van Hemel and Eussein, 2000).

This is just an example. Any of the chromosomes can be involved in the translocation with chromosome 2.



A balanced insertional translocation between chromosomes 2 and 16

From the diagram below, you can see that for a parent with a balanced insertion there are four possible outcomes when they have children. Children can have a balanced insertion like the parent; a duplication; a deletion; or usual chromosomes. Data from a large number of families show that around one third of the children will have usual chromosomes; around one third will have a balanced insertion like their parent; and around one third will have either a duplication or a deletion. These proportions vary with the size of the deletion (Van Hemel & Eussein 2000). Every case is individual and you should discuss your family's situation with your geneticist or genetic counsellor.



People with a very small deletion in certain parts of 2p also seem to be able to pass their deletion on direct to their children (Lambert 1991).

What is certain is that as a parent there is nothing you did to cause the 2p deletion and nothing you could have done to prevent it. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when they occur and nobody is at fault.

Can the 2p deletion happen again?

The possibility of having another pregnancy with a 2p deletion depends on the parents' chromosomes. If both parents have usual chromosomes, the 2p deletion is very unlikely to happen again.

If a blood test shows that either parent has a chromosome change involving 2p, the possibility is much 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.

Can my child with a 2p deletion have similarly affected children?

We know that in one family a small deletion at 2p12.2p13 was passed on and it is likely that other small deletions or microdeletions can be passed on (Lambert 1991). 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.

Potential genes involved in deletions of 2p

Chromosome 2 has been estimated to contain between 1300 and 1900 genes, that is, around eight per cent of the total amount of DNA in your cells. The major features of 2p deletions are likely to be caused by having lost one or more of these genes, acting singly or together.

The increasing use of molecular techniques such as array-CGH and FISH in research laboratories has led to more accurate definition of breakpoints in people with a 2p deletion. This has enabled researchers to identify genes which may be responsible for certain features associated with a 2p deletion.

It is important to remember that while identifying the gene(s) responsible for certain features is interesting, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is missing, it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often play a role in determining the presence or absence of a particular feature.

Genes and research

Disturbances in genes leading to holoprosencephaly

There a many different causes of holoprosencephaly and various different genetic causes. One of these is a change or loss of a gene known as SIX3 at 2p21. However, not everyone who loses this gene has holoprosencephaly, so other factors must be involved (Schell 1996; Armstrong 2006).

Holoprosencephaly is a disorder caused by the failure of part of the central nervous system to divide into left and right halves. The front part of the brain, known as the prosencephalon, fails to develop completely during fetal life. During typical development, this part of the brain is formed, and the face begins to develop in the fifth and sixth weeks of pregnancy. Holoprosencephaly is caused when the front part of the brain fails to divide completely to form the left and right halves of the brain, known as the cerebral hemispheres. The eyes, nose, palate, and upper lip can also be involved.

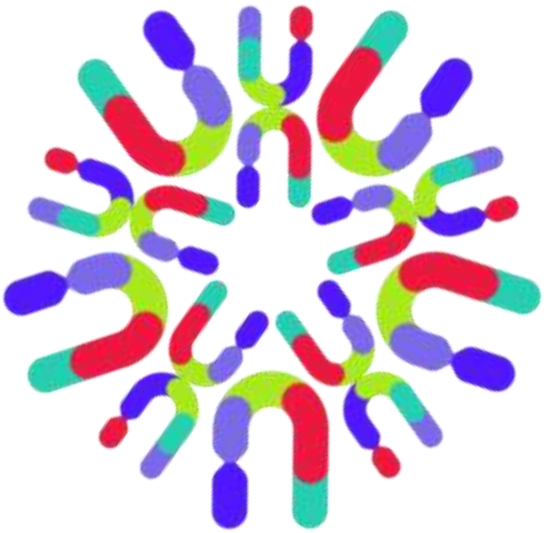
There is a vast range of severity in holoprosencephaly. At one end of the spectrum are people whose brains are to all intents and purposes unaffected but have a disruption of the midline of the face, resulting in something quite minor such as the lack of a sense of smell or a single front tooth. At the other end of the spectrum are fetuses whose brains have a single undivided front sphere.

Two genes, the MSH2 and MSH6 genes at the 2p21p16.3 junction, provide instructions for making a protein that plays an essential role in DNA repair. People who have lost these genes are believed to have an increased risk of developing a type of colon cancer and screening is recommended for early detection and treatment (Armstrong 2006; Lucci- Cordisco 2004; Sanders 2003). The SNTG2 gene at 2p25.3 is a gene that is important for the development of the central nervous system and may play a role in the learning difficulties associated with a 2p terminal or distal deletion (Gruchy 2007).
When this guide was first written, it was suggested that the NRXN1 gene at 2p16.3 could be a candidate for cognitive delay and may play a role in susceptibility to autism (Krepischi-Santos 2006; Zahir 2008). There is now further evidence that a deletion of the NRXN1 gene is associated with developmental delay and neurodevelopmental difficulties.

Unique now publishes separate guides to 2p16.3 (NRXN1) deletions

In more recent years, deletion of the SOX11 gene and MYT1L gene have been associated with separate syndromes.

Unique now publishes separate guides to Sox11 syndrome and 2p25.2 deletions and MYT1L syndrome and 2p25.3 deletions



Sources & references

The information in this leaflet is drawn from what is known about people with a 2p deletion.
Around 40 people have been described in the medical literature with a 2p deletion (2009).
The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain most articles from Unique. The leaflet also draws on information from Unique's member database. When this leaflet was written, Unique had 33 members with a deletion of 2p. Information about specific genes was added in 2021 but no other new information was added.

Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey, RH8, 9EE, UK
Tel: +44(0)1883 723356
help@rarechromo.org I rarechromo.org

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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.

This guide was compiled by Unique and has been verified by Farah Zahir, BSc (Genetics) & Killam Predoctoral Scholar, Medical Genetics Research Unit, University of British Columbia, Canada and by Professor Maj Hulten BSc, MD, PhD, FRCPath, Professor of Medical Genetics, University of Warwick, 2009. (PM). Rebranded 2026.

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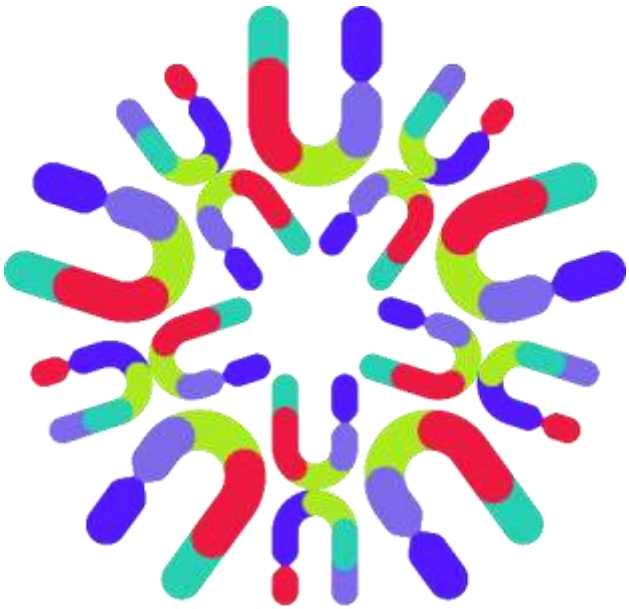

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