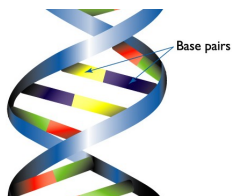


8p23 deletion syndrome



8p23 deletion syndrome

An 8p23 deletion means that the cells of the body have a small but variable amount of genetic material missing from one of their 46 chromosomes – chromosome 8. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Like most other chromosome disorders, the incorrect amount of material increases the risk of birth defects, developmental delay and learning difficulties. However, the problems vary and depend very much on what genetic material is missing.



1 base pair = bp
1,000 base pairs = 1kb
1,000,000 base pairs = 1Mb

Chromosomes are made up of DNA held together by proteins. They are rod-like structures in the nucleus of the body's cells. They carry genetic information (known as genes) that tell the body how to develop, grow and function. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. Chromosomes usually come in pairs, with one chromosome of each pair inherited from the father and the other from the mother. Of the 46 chromosomes, two are a pair of sex chromosomes, XX (a pair of X chromosomes) in females and XY (one X chromosome and one Y chromosome) in males. The remaining 44

chromosomes are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short (p) arm (shown at the top in the diagram on the next page) and a long (q) arm (the bottom part of the chromosome). People with an 8p23 deletion have one intact chromosome 8. The other 8 is missing a segment from the short arm and this can affect their learning and physical development. The size of the missing segment varies among most individuals. The clinical difficulties are very likely caused by the presence of only one copy (instead of the usual two) of a number of genes. However, a child's other genes and personality also help to determine future development, needs and achievements.

Sources

The information in this leaflet is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>). If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from two surveys of members of Unique conducted in 2004 and 2008, referenced Unique. When this leaflet was written Unique had 63 members with a pure 8p23 deletion without loss or gain of material from any other chromosome. These members range in age from babies to an adult aged 22 years. A number of other Unique members have an arrangement known as inverted duplication and deletion of 8p, in which part of the short arm is duplicated in reverse and the end of the short arm is deleted. Unique publishes a separate leaflet on this chromosome disorder, known as inv dup del 8p.

Many more people, described in the medical literature and 62 members of Unique, have a loss or gain of material from another chromosome arm as well as an 8p23 deletion, usually as a result of a chromosome change known as a translocation. As these people do not show the effects of a 'pure' deletion, they are not considered in this leaflet. Amongst Unique members the other chromosomes involved are: 1, 2, 3, 4, 5, 7, 9, 10, 12, 16, 20, 22 and X. Unique holds a list of these cases in the medical literature and the karyotypes of those in Unique; this is available on request.

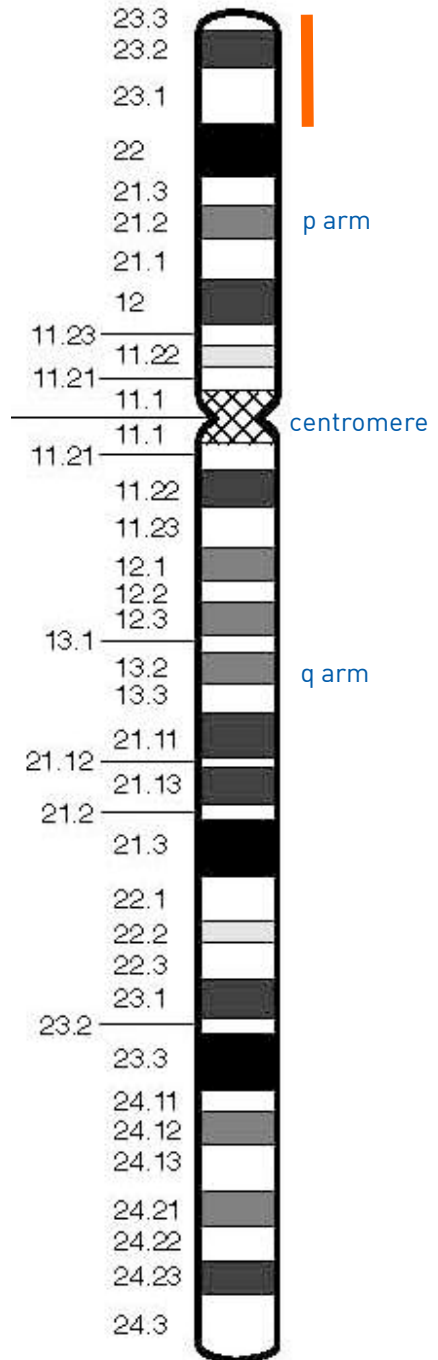
The first description of a person with an 8p23 deletion was in 1988. There have since been more than 70 people with a 'pure' 8p23 deletion (no other chromosome is involved) reported in the published medical literature. 8p23 deletions occur in equal frequency in males and females and across all ethnic groups (Fagan 1988; Wat 2009 Unique).

Looking at 8p

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 distinctive pattern of light and dark bands. 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. However, because the amount of material missing is often quite small, in this type of routine analysis your child's chromosomes may have looked normal and a number of individuals with an 8p23 deletion have needed two or more chromosome studies before the deletion was found. Consequently there are certainly people with an 8p23 deletion who have not yet been diagnosed. New, more sensitive, molecular techniques such as fluorescence in situ hybridization (FISH) testing or array comparative genomic hybridisation (array-CGH) may be necessary to confirm or detect an 8p23 deletion. Unique has an information guide on array-CGH (Claeys 1997).

In an 8p23 deletion part of the short (p) arm of chromosome 8 is missing. The majority of deletions of 8p23 are terminal. This means that the tip of the long arm is included in the deletion. However, just under half of reported 8p23 deletions are interstitial, in which a piece of the short arm of chromosome 8 is missing, but the end of the chromosome is still present (Paez 2008).

In the diagram of chromosome 8 on the right the bands are numbered outwards starting from where the short and long arms meet (the **centromere**). A low number, as in p11 in the short arm, is close to the centromere. Regions closer to the centromere are called **proximal** (or **centromeric**). A higher number, as in p23, is closer to the end of the chromosome (the telomere). Regions closer to the end of the chromosome are called **distal** (or **telomeric**).



Results of the chromosome test

Your geneticist or genetic counsellor will be able to tell you about the point(s) where the chromosome has broken in your child. You will almost certainly be given a description of your child's karyotype. With an 8p23 deletion, the results are likely to read something like the following example:

46,XX,del(8)(p23.1)dn

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material is missing
(8)	The deletion is from chromosome 8 (p23.1) The chromosome has one breakpoint in band p23.1, and material from this position to the end of the chromosome is missing
dn	The deletion occurred <i>de novo</i> (or as a 'new event'). The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 8p23. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

In addition to, or instead of a karyotype, you may be given the results of molecular analysis such as FISH or array-CGH for your child. In this case the results are likely to read something like the following example:

46,XX.ish del(8)(p23.1)(D852333-)

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
.ish	The analysis was by FISH (fluorescent <i>in situ</i> hybridisation)
del	A deletion, or material is missing
(8)	The deletion is from chromosome 8
(p23.1)	The chromosome has one breakpoint in band 8p23.1 (D852333-). The deleted part of chromosome 8 includes a stretch of DNA called D852333

arr[hg19] 8p23.3p23.1(158,046-6,999,114)x1

arr	The analysis was by array-CGH
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted
8p23.3p23.1	Chromosome 8 has two breakpoints, one in the band 8p23.3, and one in band 8p23.1
158,046-6,999,114	The base pairs between 158,046 and 6,999,114 have been shown to be deleted. Take the first long number from the second and you get 6,841,068 (6.84Mb or 684kb). This is the number of base pairs that are deleted
x1	means there is one copy of these base pairs, not two – one on each chromosome 8 – as you would normally expect

Most common features

Every person with an 8p23 deletion is unique with specific medical and developmental concerns. No one person will have all of the features listed in this leaflet. However, a number of common features have emerged:

- Heart conditions (especially when the deletion includes the *GATA-4* heart gene located in proximal 8p23.1)
- Many children will need support with learning. The amount of support needed by each child will vary
- Behavioural issues, often including hyperactivity and impulsiveness

Are there people with an 8p23 deletion who are healthy, have no major medical problems or birth defects and have developed normally?

Yes. In a few individuals the deletion seems to have a mild effect. One report in the medical literature describes a 5-year-old girl with normal intelligence. She had initial minor delays in gross motor development and language skills which were overcome. There are two reports in the literature of fathers who are unaffected by the 8p23 deletion and only discovered they carried it when they passed it on to their children.

One passed an 8p23 deletion on to his 11-year-old daughter who had mild learning difficulties and her 7-year-old brother who was more severely affected with moderate learning difficulties. The second, a 38-year-old man, passed the 8p23 deletion on to his daughter who at 6 months old was also unaffected. A 22-year-old unaffected mother passed an interstitial 8p23.1p23.2 deletion on to a son, who was also unaffected, and a daughter who had moderate learning difficulties, deafness and a heart condition (Pettenati 1992; Reddy 1999; Barber, personal communication).

What is the outlook?

Healthwise, most children do well. The most significant medical concern that can affect lifespan is the heart anomalies that are often seen in children with an 8p23 deletion. In the vast majority of children the heart problems are not severe and if necessary can be corrected surgically. Sadly, however, there are a number of babies in the medical literature who have died shortly after birth or in the neonatal period due to severe heart

problems or respiratory distress. No Unique member with a pure 8p23 deletion has died (Unique).

Assuming that the child is not severely affected by a heart condition, lifespan is likely to be normal and there is no reason why adults should not lead supported independent lives. There are a number of adults in the medical literature whose 8p23.1 deletion was found by chance (see preceding section and [Adults with an 8p23 deletion](#) page 17). Unique has members who are virtually unaffected by their 8p23 (Pettenati 1992; Reddy 1999; Unique).



11 years

Pregnancy

The majority of mothers carrying babies with a deletion of 8p23 experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. Of the 14 families who participated in the Unique survey and have told us about their pregnancy experiences, two babies showed reduced fetal movement. One mother had elevated levels of alpha-fetoprotein (AFP; a protein produced by the unborn baby which is often used as a screening test for a number of disorders), but all prenatal ultrasound scans were normal. Another mother developed a pregnancy induced allergy to dairy products (Devriendt 1999; Unique).

Two Unique babies were diagnosed with an 8p23 deletion prenatally by amniocentesis. There are also several examples in the medical literature of prenatal diagnosis of an 8p23 deletion by amniocentesis performed after fetal anomalies, such as cardiac anomalies, were detected on prenatal ultrasounds. In three cases, the parents chose not to continue with the pregnancy. In the fourth case, no anomalies were seen on the ultrasound scan and the father carried the same 8p23 deletion and was unaffected. The parents chose to continue with the pregnancy and a healthy baby girl was born. At 6 months old she was unaffected by the deletion (Faivre 1998; Bhatia 1999; Reddy 1999; Unique).

However, a small number of babies reported in the medical literature had amniocentesis, performed either for maternal age or after detection of fetal anomalies on an ultrasound scan, which failed to detect the 8p23 deletion. This may be partly explained because 8p23 deletions are often small and easier to see in high resolution postnatal chromosomes than in the lower resolution chromosomes typical in prenatal samples. Additional tests may be needed to confirm that a deletion is present (Pecile 1990; Wu 1996; Baynam 2008).

Feeding and growth

Babies are often small and underweight at birth. The published medical literature reports that more than half of all babies have low birth weight. Birth weights recorded at Unique show considerable variation with an average of 3.05 kilos (6lb 12oz) (Digilio 1998; Paez 2008; Unique).

Range of birth weights at Unique (at or near term):

2.21 kilos (4lb 14oz) to 4.05 kilos (8lb 15oz)

Medical reports suggest that around half of all babies showed slow growth after birth. Feeding difficulties can be an area of concern for families, particularly as babies may start out small and underweight. Some babies have difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft or high palate can also find the action of sucking and swallowing difficult. Seven of the 21 mothers surveyed by Unique attempted to breastfeed their babies. One had difficulties and moved onto bottle feeding after a few weeks but the others were successful and breastfed their babies until weaning onto solid foods. Two Unique children had a temporary gastrostomy tube placed (a G-tube, feeding direct into the stomach). A small number of children are affected by gastro-oesophageal reflux (in which feeds return readily up the food passage). In the

Unique survey, two out of 14 babies had reflux. This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Devriendt 1995; Digilio 1998; Unique).



Second birthday

Some older babies and toddlers have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers and the start of finger feeding may be delayed. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems (Unique).

In spite of any early feeding troubles and/or low birth weight, the majority of children with an 8p23 deletion have normal growth with a number of Unique children being described as 'very tall' for their age. Indeed, once past babyhood, appetite does not seem to be a problem. On the contrary, a few children develop a big appetite and are said to love food. A very small minority of Unique children became heavy and overweight (Unique).

“ She was slow to feed at first but soon got the hang of it and was bottle fed. Solids were a major issue and she didn't learn to chew properly until after her second birthday. She sometimes still prefers not to have lumps in her food – 3 years

Appearance

Most children with an 8p23 deletion look little different to other children and closely resemble their siblings or parents. Others, perhaps particularly those with a larger deletion, have facial features in common. The most common feature is microcephaly (a small head), which affects a third to half of all children with an 8p23 deletion. They may also have a high, narrow forehead, a broad nasal bridge and a short neck. Their ears may be low-set and unusually formed. There may be an extra fold of skin covering the inner corner of the eye (epicanthic folds). Some children with an 8p23 deletion have a broad chest with wide-set nipples. (Unique).

“ He has no unusual features – he looks just like other family members – 2½ years

Learning

Typically, children with an 8p23 deletion experience mild learning difficulties. As always, there is individual variation with a minority of individuals with no learning difficulties at all and, very rarely, children who are severely affected. The Unique experience is that the majority have a mild or mild-moderate learning difficulty. One of the 21 surveyed children had a severe learning difficulty and two, a 12-year-old boy and an 11-year-old girl, have no learning difficulties at all. Two Unique members have graduated from mainstream school and are currently attending college. Another Unique member is taking a life skills course at college. Around half of those at Unique attend a mainstream school, often benefiting from an attached special needs unit or 1:1 assistance in the classroom. The other half attend a special educational needs school (Gilmore 2001; Unique).

Within this picture certain common features have been noticed. Children with an 8p23 deletion are often easily distractible and have trouble concentrating which can make learning more of a challenge. However, many Unique children are described as having a good memory. Many Unique children have mastered reading to some degree: some can recognise their name and some basic words; others love to read. Although many Unique children experience difficulties with handwriting due to poor fine motor skills (see [Development: hand-eye co-ordination and dexterity \(fine motor skills\)](#) page 11), writing and drawing has also been achieved by the majority of children. Many parents note that the most successful methods for learning involve learning through play and making learning fun. Children need plenty of praise and encouragement. Children with an 8p23 deletion seem to share a passion for music and singing (Paez 2008; Unique).

“ She is doing really well at nursery. She enjoys music, dancing and stories – 3 years

“ He is very bright but needs constant attention due to his behaviour. His memory is very acute – 4½ years

“ She scribbles and can draw a balloon shape and a rough face – 8 years

“ She has a wonderful imagination and loves role play and imaginary play. She loves music and singing. She has a good ear for music, but struggles to learn the words of songs. She is quite able on the computer – 11 years

“ He never forgets anything. He is very clever and in the second set at school for maths and English – 12½ years

“ She is doing OK in [special] school: average or below average for most subjects. She can write but it is illegible unless on a line and prompted – 13 years

“ It is an effort for him to read but in the last 2 years he even tries to read the local newspaper and tries to make out what post we receive. He enjoys word searches, colouring in and drawing pictures – 14½ years

“ She reads really well. She benefits from one to one assistance as it helps her gain a bit more concentration. She still can only concentrate for a while but it is a lot better than it was. She has come a long way. She left school with a GCSE in Art and 6 passes at Entry level 3. She is now at 6th form college doing a course in life skills – 17 years

“ She has never given up. She is a stronger reader now, although she does not yet read for pleasure – 22 years

Speech and communication

Evidence from both the medical literature and from Unique show that children typically start to speak late with first words arriving after the age of 2 years. The majority of children have a mild or moderate delay in both understanding and expressive speech but by school age most children have overcome this delay and are maturing into complex speakers and users of language. The medical literature describes a 14-year-old who is bilingual. However, within this picture there is considerable variation with reports of children who have no speech delay to those who are severely delayed.

A small minority continue to use single words and retain a severe delay in understanding (Unique).

The picture exchange communication system (PECS) and/or sign language can help children communicate their needs. Many Unique children utilise these methods and make good, steady progress. For most, as speech develops they find they no longer have any need for sign language. The initial delay with certain sounds can make some children's speech hard to understand. Speech therapy can be enormously beneficial, enabling some children whose speech is initially delayed to master clear speech with good articulation, vocabulary and sentences (Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. Those with a cleft or high palate may also have specific difficulty with certain sounds (Unique).

“ She uses some signs, but her speech is improving slowly. She is starting to put two or three words together such as ‘I see’, ‘my baby’ and ‘where gone?’. Her speech is not very clear – *3 years*

“ Speech has come a long way and he is now able to speak in sentences although he has some difficulties with articulation and finds sounds that use the tongue at the front of the mouth difficult to make – *4½ years*

“ She is capable of having a simple childlike conversation. Her vocabulary is broad – *11 years*

“ Her language is rote and simple, but more than adequate and functional – *13 years*

“ He has been through 3 years of a communication class in school that has really helped his speech and he now speaks in almost complete sentences – *13 years*

“ He has excellent oral communication although he does attend speech therapy for not interrupting others, making good eye contact and staying on topic – *14½ years*

“ He speaks in sentences but sometimes it is hard to understand what he is saying – *16½ years*

“ Her speech is normal. In the early years she was quite slow to talk and had speech therapy at *3½ years* – *17 years*

“ He learned to speak at *3-3½ years* and now his speech is fine. Every once in a while a word is hard to pronounce – *19 years*

“ He has full speech with a large vocabulary – *21 years*

Development: sitting, moving, walking (gross motor skills)

For some children, early developmental milestones are reached at an appropriate age although mild delays are not uncommon. The Unique experience is that babies start to roll between 3 and 18 months (at an average of 8 months); sit between 5 and 16 months (average 8½ months) and crawl between 6 months and 2 years (average 13 months). Walking was mastered between 13 months and 2½ years (average 19 months) (Unique).

These delays may be attributed to hypotonia (floppiness or low muscle tone) or hypertonia (an increase in tightness of muscle tone and a reduced ability of a muscle to stretch) that can affect those with an 8p23 deletion.

Physiotherapy has proved beneficial to many children. Difficulties with hand-eye co-ordination, planning and organisation and poor balance can also contribute to these delays. The continuing difficulties with balance mean that some children are unsteady on their feet and fall easily. One Unique girl practises yoga to improve her balance (Unique).

Many children progress to running, jumping, throwing and catching and climbing. A number of Unique children are very active and love all sports. Physical activities enjoyed by Unique children include swimming, riding a bike or scooter, playing ball games (including baseball and football), horse-riding, archery, sailing and gymnastics. However, some children tire easily and find sports and sustained exercise a challenge (Unique).



3 years

“ He crawled at 18 months and walked at 2 years. He still crawls up and down stairs but can walk up if holding someone’s hand – *2½ years*

“ She walks and crawls. When she is walking she falls frequently and has a very clumsy gait. She appears not see objects in front of her so walks into things all the time. She has no sense of danger – *3 years*

“ She walks and runs but is very unsteady and unco-ordinated going down stairs. She uses a wheelchair if going out for a walk as she gets tired very quickly – *8 years*

“ Her feet taper and she has an immature gait and can be unsteady on her feet. She has hypertonia and her thighs and calves are solid – *11 years*

“ He has no mobility problems. He is a very active boy who loves sports – *12½ years*

“ His run is very clumsy and he falls if he runs too fast – *13 years*

“ In general her co-ordination is behind her peers. She learned to ride a bike by the age of 5 years – *now 22 years*

Development: hand-eye co-ordination and dexterity (fine motor skills) and self care

Fine motor skills in children with an 8p23 deletion are often affected and they may take longer to reach for and grab toys and hold a bottle or cup. Problems with balance and co-ordination also contribute to these delays. Together, this can lead to delays in children being able to self-feed and hold a pen to write or draw. Holding and controlling a writing implement is often especially problematic with many children experiencing handwriting difficulties. For these children mastering a keyboard can often be easier. Many children have occupational therapy in order to help improve these skills (Unique).

As a result of these difficulties, children are likely to continue to need help with dressing and undressing (zips, buttons and shoelaces can be especially problematic). They may also continue to require assistance in tasks such as brushing teeth and washing for longer than their peers. The information at Unique and in the medical literature shows that consistent toilet training was mastered between 13 months and 6 years (at an average of 3½ years) (Gilmore 2001; Paez 2008; Unique).

“ He has only recently obtained fine pincer grip and he struggles with stacking blocks – *2½ years*

“ She finds it difficult to hold and use cutlery and has trouble manipulating some toys – *3 years*

“ She is still in nappies all of the time and she needs help cleaning her teeth, washing and getting dressed – *8 years*

“ Her co-ordination and dexterity are very poor. Her writing is poor, she is a messy eater and cannot do up buttons or zips – *11 years*

“ She is self-sufficient but needs supervision. If left to herself, she would never brush or wash! – *13 years*

“ He cannot brush his teeth but can dress himself a little. He still needs help with trousers, shoes and jackets but can work a CD or DVD player with ease! – *13 years*

“ He can wash himself and brush his teeth but he struggles to do up buttons and with tying his shoe laces – *16½ years*

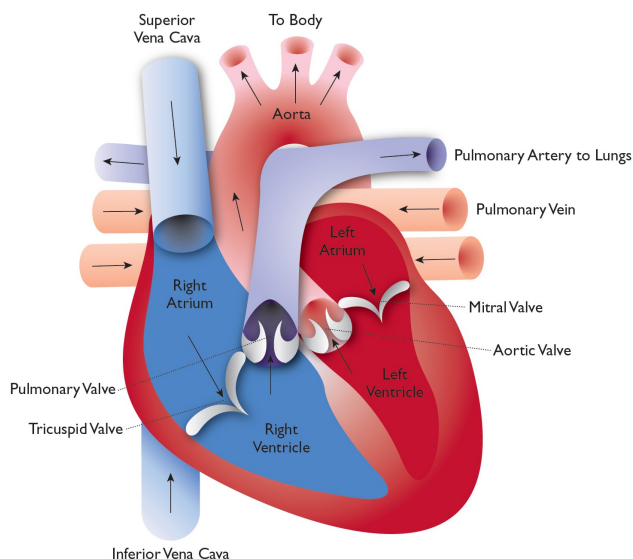
“ She was out of nappies at 18 months. She can dress herself and keep herself clean and tidy. She needs supervision in the bath and has help washing her hair – *17 years*

“ His dexterity is slow and he needs more time for writing and grasping – *21 years*

Medical concerns

■ Heart conditions

Heart conditions are common, having been observed in around 60 per cent of Unique babies with an 8p23 deletion. The medical literature reports that heart defects occur in 75 per cent of children with a terminal deletion of 8p23 deletion and 94 per cent of those with an interstitial deletion. The evidence at Unique is that 38 per cent have a complex heart condition which necessitated surgery, 24 per cent have a mild condition that has either healed spontaneously or is expected to and 38 per cent have no heart condition at all (Paez 2008; Wat 2009; Unique). Heart conditions have been attributed to deletion of a single gene (called GATA4 which stands for GATA binding protein 4) that lies in the proximal part of band 8p23.1 If an 8p23.1 deletion removes a copy of this gene, a heart condition is likely but not inevitable. If the deletion does not remove a copy of this gene, a

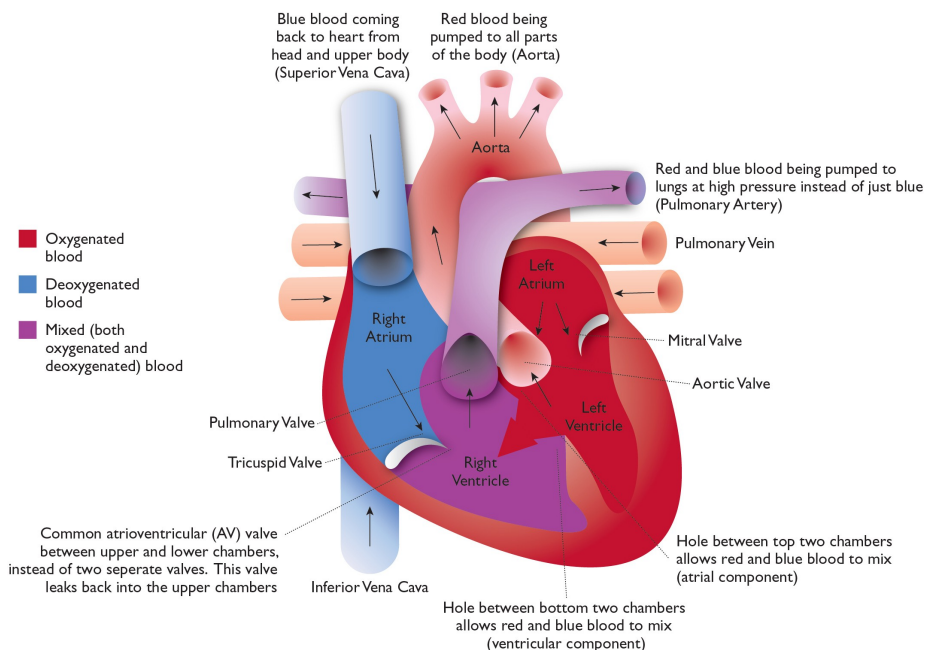


A normal heart

heart condition is much less likely but not impossible (see section [Ongoing Research involving 8p23](#), page 18).

A wide spectrum of heart defects have been reported. The characteristic heart defect seen in children with an 8p23 deletion is atrioventricular septal defect (AVSD) which is also known as atrioventricular canal (AVC) and accounts for almost half of the heart conditions seen in children with an 8p23 deletion. AVSD results from the failure of formation of the part of the heart that arises from an embryonic structure called the

endocardial cushions (see diagram). The endocardial cushions are responsible for



AVSD

separating the central parts of the heart near the tricuspid and mitral valves (AV valves), which separate the atria from the ventricles. The structures that develop from the endocardial cushions include the lower part of the atrial septum (wall that divides the right atrium from the left atrium) and the ventricular septum (wall that divides the right ventricle from the left ventricle) just below the tricuspid and mitral valves. The endocardial cushions also complete the separation of the mitral and tricuspid valves by dividing the single valve between the embryonic atria and ventricles. This leaves an opening in the centre of heart and sometimes a single valve instead of the two separate valves that usually separate the upper and lower heart chambers. This opening allows oxygen-rich blood travel back through the lungs, making the heart pump harder to get enough oxygen-rich blood around the body. Surgery is needed to correct the AVSD (Faivre 1998; Paez 2008; Unique).

Other heart defects that are reported to affect children with an 8p23 deletion include pulmonary stenosis (a narrowing of the pulmonary valve, meaning that the heart has to work harder to pump blood which results in breathlessness); atrial septal defects (ASD; a hole in the muscular wall between the two filling parts of the heart, the atria); ventricular septal defects (VSD; a hole in the wall between the two pumping chambers of the heart, the ventricles) and hypoplastic left heart syndrome (the left side of the heart has not developed properly and is very small. The aorta, the artery that carries blood from the heart around the body, is tiny and blood can only reach it through the ductus arteriosus, a blood vessel that normally closes within days of birth).

Reported more rarely, in only a handful of children including two Unique babies, is Ebstein's anomaly, a heart defect affecting the right side of the heart. The tricuspid valve that controls blood flow from the top chamber (atrium) to the bottom (ventricle) is too low down. This makes the top chamber too big and the bottom chamber too small. The valve may also be leaky, letting blood that should be in the ventricle leak back into the atrium. Tetralogy of Fallot (the artery that takes the blood to the lungs has an unusually narrow entrance (pulmonary stenosis), and there is also a VSD) affected one Unique baby and has been reported in the medical literature to affect three babies (Digilio 1998; Giglio 2000; Paez 2008; Wat 2009; Unique).

■ Congenital diaphragmatic hernia

A number of children with 8p23 deletions have been diagnosed with a congenital diaphragmatic hernia (CDH), where there is a hole in the muscular wall (the diaphragm) which separates the heart and lungs from the contents of the abdomen. This hole is normally present in a baby during early development and usually closes by the end of the third month of pregnancy. In CDH, the hole has stayed open which may allow some of the contents of the abdomen (including the stomach, intestines, spleen and liver) to move up through the hole and into the chest cavity potentially depriving the lungs of space to develop properly. This means that the lungs may be smaller than they should be. Additionally, CDH may also stop the heart from growing normally. Newborn babies with CDH may have respiratory distress and may require oxygen and /or breathing assistance. Surgery is often necessary to repair the hole. One study reported that 22 per cent of children with an interstitial 8p23 deletion and eight per cent of children with a terminal 8p23 deletion are affected. The evidence at Unique is that around 20 per cent of children have been diagnosed with a CDH (Wat 2009; Unique).

■ Palate

A high arched palate (the roof of the mouth) was seen in around 30 per cent of surveyed Unique children. In one study in the published medical literature almost 60 per cent of children were affected. One Unique child had a cleft palate (the palate does not form correctly during development, which results in an opening in the roof of the mouth). Both cleft and high palates can contribute to the early feeding difficulties seen in children. A high palate can make latching on and sucking more difficult and a nipple shield or, if bottle-fed, a variable-flow teat can help. Palate anomalies may also make speech and making the sounds of speech more difficult (Digilio 1998; Unique).

■ Breathing

Asthma affects a number of Unique children with an 8p23 deletion. In children with asthma, the airways occasionally constrict, become inflamed, and are lined with excessive amounts of mucus with wheezing, shortness of breath, chest tightness, and coughing. Children with an 8p23 deletion are often affected only mildly and the asthma frequently improves as children grow up. One Unique child has frequent colds and infections which cause breathing problems and she gets 'wheezy' very easily (Unique).

■ Skin

Eczema is a type of allergic reaction that seems to affect a number of children with an 8p23 deletion. In mild forms the skin is dry and itchy, whilst in more severe forms the skin can become broken, raw and bleeding. Gentle moisturising creams and emollients can help keep it under control. Prescribed steroid creams can be employed in more severe cases (Unique).

■ Vision

It is not clear if an 8p23 deletion has a direct effect on vision. Over 50 per cent of those who took part in the Unique survey had a vision problem. However, there is a wide range of problems, the most common of which are a squint (strabismus) and long sight. Short sight has also been reported. A Unique brother and sister each with an 8p23 deletion have both been diagnosed with some peripheral vision loss.

The 22-year-old sister wears glasses and needs breaks from reading as her eyes tire easily. The 19-year-old brother also has problems with depth perception. He wears glasses and does eye exercises. His eyesight has improved and he has been approved to apply for a driving licence (Blennow 1990; Hutchinson 1992; Unique).



10 years

■ Feet

People with an 8p23 deletion often have feet that are not properly formed. Evidence at Unique suggests that a number of children are flat-footed: the arch of the foot has collapsed resulting in the entire sole of the foot coming into contact with the ground. In some cases this has necessitated wearing orthotics, insoles in the shoes or supportive footwear. Other Unique children have feet or ankles that turn slightly in, overlapping toes, syndactyly (toes that are joined together) or feet that taper.

One Unique child's toes are growing outwards causing bunions. The hypotonia that affects some children with an 8p23 deletion may contribute to the feet and ankle problems (Unique).

■ Minor genital abnormalities

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys. These include cryptorchidism (undescended testes) and hypospadias, where the hole usually sited at the end of the penis is on the underside instead. In some cases, surgery may be needed to correct these concerns. One Unique boy had testes that descended late and two Unique boys had micropenis (a small penis) (Digilio 1998; Unique).

■ Seizures/Epilepsy

A few children are reported in the medical literature to have seizures, which may be absence seizures (a brief loss of awareness for several seconds) or occur after surgery or trauma. Only one child who took part in the Unique survey suffered absence seizures and they were controlled by medication (Claeys 1997; Digilio 1998; Paez 2008; Unique).

■ Infections

More than a third of those children who participated in the Unique survey were reported as suffering from frequent infections (Unique).

■ Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers so regular and high quality dental care is important (Unique).



4 years



6 years

Behaviour

Many children with an 8p23 deletion are happy, sociable and affectionate. However, a significant number of children – although not all – show a similar pattern of behavioural difficulties. Typically they display sudden and extreme changes of behaviour, with outbursts of aggressiveness and destructive behaviour. This behaviour can be directed at themselves and others and include hair pulling, hitting, biting and kicking. They are often immature, easily frustrated and can be impulsive. They tend to be hyperactive with poor concentration, a short attention span and are easily distracted, all of which can make learning more challenging. Two of the fourteen who took part in the 2008 survey have been diagnosed with attention deficit hyperactivity disorder (ADHD) which is characterised by restlessness and a short attention span. The survey also identified one Unique child who had been diagnosed with autism or pervasive developmental disorder (PDD) which can affect a child's ability to communicate, understand language, play, and relate to others. For some parents children with challenging behaviour have responded well to standard discipline techniques such as ignoring unwanted behaviour and rewarding them with cuddles and attention when they stop. Other children, however, required medication in order to manage the behaviour and allow to children to concentrate better and interact with their peers (Claeys 1997; Unique).

These behavioural problems frequently emerge by toddler or primary school age. Some parents report that behavioural problems increase around puberty. However, on a more positive note, there is evidence that behavioural problems in children with an 8p23 deletion are a phase that they grow out of. Follow-up on one child in the medical literature showed that at the age of 16 years the behavioural problems had largely disappeared. Evidence at Unique backs this up with many children's behaviour improving as they grow up. A 12-year-old boy who had behavioural difficulties when younger (including aggressiveness, hitting and unco-operativeness) was described as being 'a pleasure to know'. He is very polite with good manners and very happy and upbeat. A 21-year-old's behaviour improved when he was 17 years old (Claeys 1997; Unique).

"She enjoys playing with her brother but not for long. She doesn't really get on with other children although this is slowly improving – 3 years"

"He has been diagnosed with ADHD. He shows inappropriate friendliness and can hit, bite and push his peers. He takes a long time to get re-focused if he gets angry – 4½ years"

"She is very changeable, from very sweet and charming to the complete opposite – 8 years"

"She is very sociable and interacts well with all age groups, although she can overwhelm small children. She needs a lot of attention, interaction and care. She can be very demanding and egocentric. She is noisy and untidy. But she is loving and generous, compassionate and caring, innocent and cute, funny and adorable and a valued member of our family! – 11 years"

"She is impulsive, immature and does not know social cues or responses – 13 years"

"He has ADHD and has a lot of energy throughout the day. At school he scratches, slaps and kicks the teachers and other children. This behaviour is not seen outside of school – 13 years"

"He has no major tantrums and those he does have we have been able to talk him out of. He has always been full of life and happy and loving. He is eager to please, helpful and considerate of others – 14½ years"

“ He helps with all the chores around the house and enjoys grocery shopping. He is very pleasant to be with. He was in Boy Scouts since he was little and became an Eagle Scout when he was 18 – *19 years*

“ He had a lot of behavioural problems that he grew out of at about 17 years of age. He is learning to drive and is very social with a good sense of humour – *21 years*

“ She easily becomes frustrated. She is doing better as she matures – *22 years*

Puberty and Fertility

From the limited information that is available, puberty generally appears to occur at the normal time and to proceed as expected. However, there are reports of precocious (early) puberty in the published medical literature: puberty began at 7½ years in one boy and a girl had pubic hair 7 years although by 8½ years she had no further signs of puberty (Blennow 1990; Hutchison 1992; Paez 2008; Unique).

There are at least two reports of fathers passing on an 8p23 deletion to their children. There is also one mother who has passed an 8p23.1p23.2 deletion onto a son and daughter (Pettenati 1992; Reddy 1999; Barber, personal communication).

Adults with an 8p23 deletion

Unique has 6 adult members including a 22-year-old woman who has a non-verbal learning disorder but has graduated from mainstream school and has spent 10 months living abroad. She is currently attending college where she is doing well and keeping up with her peers. She likes museums and travelling. Her 19-year-old brother, who also has an 8p23 deletion and moderate learning difficulties, has also graduated from mainstream school and is attending college. A 21-year-old man had a lot of behavioural problems as a child but he grew out of them at around 17 years of age. He works as a labourer in a flooring business and helps out on the family farm. He is learning to drive and is very sociable. He lives at home but travels alone on trains and buses (Unique).

The adults reported in the published medical literature include two fathers who are unaffected by the 8p23 deletion. One is a 38-year-old electrical engineer who only discovered he had a deletion of 8p23.1 when his unborn daughter was found to have an 8p23.1 deletion. A mother passed an 8p23.1p23.2 deletion on to her son, who was also unaffected and also to her 22-year-old daughter who was deaf, had moderate learning difficulties and pulmonary stenosis. Also reported in the medical literature is a 29-year-old woman who is described as having no heart problems but has suffered recurrent miscarriages and a 27-year-old woman has mild learning difficulties and who had growth delay in childhood. She had an ASD that was corrected at the age of 3 years. At 27 years she was affected by scoliosis (curvature of the spine) for which she wore a brace (Pettenati 1992; Pehlivan 1999; Reddy 1999; Barber, personal communication).



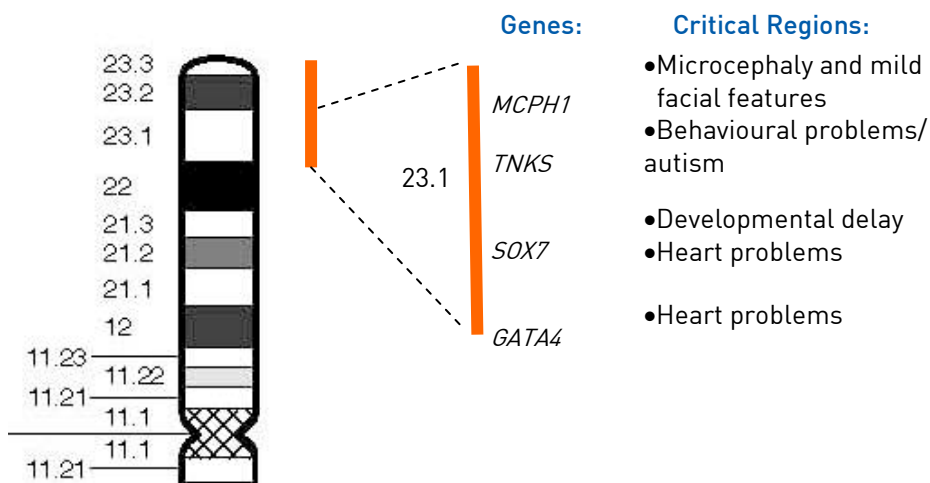
21 years

Ongoing research involving 8p23

A broad clinical spectrum from normal intelligence to severe learning disabilities and minor to severe organ malformations has meant that characterisation of 8p23 deletions

has been elusive. The features of an 8p23 deletion are likely to be a result of the loss of a number of different genes found in this region. The variable picture could be explained by the extent of the deletion or variation in the breakpoints. There is some evidence that people with a breakpoint closer to 8p23.2 and the end of the short arm may be less severely affected. Additionally it has been suggested that the extent of learning difficulties is related to the size of the deletion (Hutchison 1992; Digilio 1993; Reddy 1999).

Since deletions of 8p23 are associated with a high incidence of cardiac anomalies this has led to the suggestion that this region of chromosome 8 may harbour a gene important in heart development. To this end researchers have studied people who have an 8p23 deletion and attempted to determine the region of chromosome 8p23 that is responsible for heart problems. These studies have identified a critical region that, when missing, is responsible for the heart defects (see diagram below). This region includes the *GATA4* gene which codes for a protein that is expressed in the heart. Recent experiments in mice have also demonstrated the importance of *GATA4* in heart development. Hence, *GATA4* has been put forward as a possible gene responsible for the cardiac anomalies that often accompany an 8p23 deletion. A recent study proposes that another gene, *SOX7* (which is expressed in the heart and is thought to function in the same pathway as *GATA4*), as contributing to the heart anomalies in people with an 8p23 deletion. *SOX7* has also been proposed as having a role in the developmental delay and possibly the microcephaly and facial features seen in those with 8p23 deletions (Digilio 1993; Bhatia 1999; Devriendt 1999; Pehlivan 1999; Zeisberg 2005; Paez 2008; Wat 2009).



Studies have also been attempted to find a critical region for the behavioural problems associated with 8p23 deletions and have proposed a gene, *TNKS* (*Tankyrase 1*), as responsible for the behavioural problems and learning difficulties because it is highly expressed in the brain. However, the same *TNKS* gene has also been suggested as responsible for the diaphragmatic hernias seen in some people with 8p23 deletions. The *MCPH1* (microcephalin 1) gene has been implicated in autism, microcephaly and developmental delay (Devriendt 1999; Baynam 2008; Paez 2008; Ozgen 2009).

It is also important to remember that while identifying the responsible gene(s) is

interesting, it does not yet lead directly to improved treatment. Additionally, even if the supposedly responsible gene is missing it does not mean that the feature will necessarily be present. Other genetic and environmental factors may have a role in determining the presence or absence of a particular feature.

Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 8p23 deletion occurred in the child. In the majority of cases 8p23 deletions occur when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn). *De novo* 8p23 deletions are caused by a change that occurred when the parents' sperm or egg cells were formed. Some 8p23 deletions are accompanied by a gain of material from another chromosome and are the result of a rearrangement in one parent's chromosomes. This is usually a rearrangement known as a balanced translocation in which 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.

Balanced translocations involving one or more chromosomes are not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers. Whether the deletion is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 8p23 deletion and nothing you could have done would have prevented it occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. It is no-one's fault.

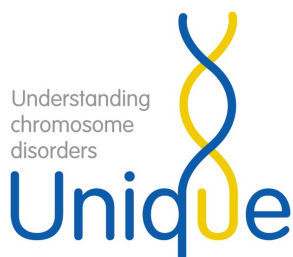
In recent years, more insight has grown in how deletions may occur. More specifically, it was realized that some people carry a deletion which is the same size and is located at the same position on chromosome 8p23.1. This region appears to be a weak spot in the chromosome, which more frequently than other regions, may result in the loss of this part of chromosome 8p. The same has been observed for several other chromosomal regions (Giglio 2001).

Can it happen again?

The possibility of having another pregnancy with an 8p23 deletion depends on the parents' chromosomes. If both parents have normal chromosomes when their blood cells are tested, the deletion is very unlikely to happen again. However, there is a very small possibility that the deletion occurred early during the formation of the egg or sperm cells in a parent. When this occurs there is a tiny chance that parents with apparently normal chromosomes could have another affected pregnancy. This is called gonadal mosaicism. However, this is exceptional, thus far not described for the deletion in chromosome 8p, and therefore the chance of recurrence is generally low.

On the other hand, if either parent has a chromosome rearrangement or deletion involving 8p23, the possibility is greatly increased of having other affected pregnancies. Parents should have the opportunity to meet a genetic counsellor to discuss the specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of in vitro fertilisation and embryo biopsy, and only healthy embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all of these tests are available in all parts of the world.

Inform Network Support



Rare Chromosome Disorder Support Group,

PO Box 2189, Caterham, Surrey CR3 5GN, UK

Tel/Fax: +44(0)1883 330766

info@rarechromo.org | www.rarechromo.org

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Please help us to help you!

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. It was compiled by Unique and reviewed by Professor Koenraad Devriendt, University of Leuven, Belgium, Dr John Barber, Deputy Director, Wessex Regional Genetics Laboratory, Salisbury, UK and by Professor Maj Hultén BSc, PhD, MD, FRCPath, Professor of Medical Genetics, University of Warwick, UK. 2009, 2010, 2013

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