Understanding chromosome disorders

Unique

8p23 duplication syndrome

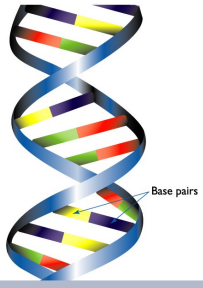
rarechromo.org

8p23.1 duplication syndrome

An 8p23.1 duplication is a very rare genetic condition in which there is a tiny extra piece from one of the 46 chromosomes – chromosome 8.

Chromosomes are made up mostly of DNA and are the structures in the nucleus of the body's cells that carry genetic information (known as genes), telling the body how to develop, grow and function. Chromosomes usually come in pairs: one chromosome from each parent. Of these 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 on the left in the diagram below) and a long (q) arm (on the right). Generally speaking, for correct development the right amount of genetic material is needed – not too little and not too much. However, a child's other genes and personality also help to determine future development, needs and achievements.

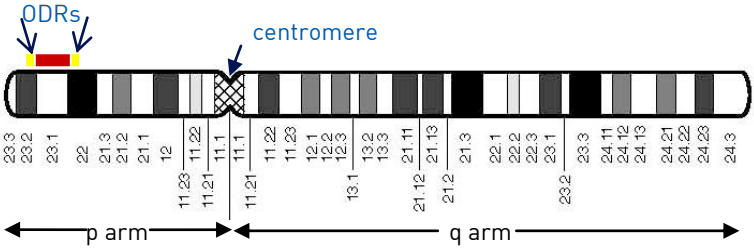
Looking at chromosome 8p23.1



You can't see chromosomes with the naked eye, but if you stain them and magnify them under a microscope, you can see that each one has a distinctive pattern of light and dark bands (see diagram below). Band 8p23.1 contains around 6.5 million base pairs. This sounds like a lot, but it is actually quite small and is only 0.2 per cent of the DNA in each cell and only four per cent of the DNA on chromosome 8. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure.

You can see from the diagram below that at each end of band 8p23.1 there are some highly repetitive regions of DNA which are called the olfactory receptor/defensin repeats or ODRs. Many people have extra copies of these repetitive regions (the ODRs) without having an extra piece of the band 8p23.1 that lies between the repeats. People who have extra copies of just these ODRs generally have no health problems and develop normally. However, under a microscope, it is not possible to tell the difference between having extra copies of the ODRs and having an extra piece of the piece of the band 8p23.1 that lies between the repeats. A molecular technique called array comparative genomic hybridisation (array-CGH) is needed to distinguish the difference between a duplication of 8p23.1 and extra copies of the ODRs only.

bp	= base pair
kb	= kilobase pair or 1000 base pairs
Mb	= megabase pair or 1 million base



Sources

The information in this guide 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 (www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from Unique. In addition, this guide draws on information from a survey of members of Unique conducted in 2011, referenced Unique. When this guide was written Unique had ten members with a pure 8p23 duplication (no other chromosome is involved). These members range in age from a child of two years to an adult aged 47 years.

8p23.1 duplications are often referred to as 8p23.1 duplication syndrome and were first described in 2005. At present 11 people with 8p23.1 duplication syndrome have been described in the medical literature (Barber 2005; Barber 2008; Barber 2010). Many more people have a different disorder known as 8p23.1 deletion syndrome where the same piece of band 8p23.1 between the repeats is not extra but is missing. Unique publishes a separate information guide to 8p23.1 deletion syndrome.

Array CGH report

Your geneticist or genetic counsellor will be able to tell you about the position at which the extra material can be found on the chromosome 8 of your child. With 8p23.1 duplication syndrome, the formal results are likely to read something like the following example:

arr [hg19] 8p23.1 (7256029-12285664)x3

arr	The analysis was by array (arr) comparative genomic hybridisation (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
8p23.1	The chromosome involved is number 8 and the band numbered 23.1 in the short (p) arm
(7256029-12285664)x3	An extra piece of DNA between the base pairs 7,256,029 (around 7 million base pairs [Mb] from the top of the short arm) and 12,285,664 (around [12 Mb] from the top of the short arm) has been found. Take the first long number from the second and you get 5,029,635 (approximately 5 Mb). This is the number of base pairs that are duplicated. The x3 means there are three copies of this piece of band 8p23.1, not two – one on each chromosome 8 – as you would normally expect

Main features

When only very small numbers of people have been identified, we can't yet be certain what the full range of possible effects of the duplication are. The features are variable but include one or more of the following:

- Speech delay
- Children are likely to need support with learning. The amount of support needed by each child will vary, although most benefit from supportive services for special needs
- Heart problems

How common is 8p23.1 duplication syndrome?

It has been estimated to affect 1 person in every 64,000 (Barber 2010).

What is the outlook?

We can't be sure yet, but there appears to be no reason why people who are healthy should not enjoy a normal lifespan. Three adults have been described in medical literature and Unique has one adult member (see page 10).

Pregnancy

Most mothers carrying babies with an 8p23.1 duplication experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, four out of 11 people described in medical literature were diagnosed by a chromosome test prenatally. Two babies were diagnosed prenatally after amniocentesis due to advanced maternal age (Barber 2010). In one of these cases, subsequent tests on other family members revealed that the duplication was also present in the father (who was described as 'slow' and had a hearing loss in both ears) and in an older sibling who had global developmental delay, speech delay and behavioural difficulties. The parents chose not to continue the pregnancy. Another mother had an amniocentesis and chromosome analysis after a heart defect was detected at a prenatal ultrasound scan at 21 weeks (Barber 2010). One baby was diagnosed by chromosome analysis when amniocentesis was performed after biochemical screening suggested an increased risk of Down's syndrome (Barber 2008).

One mother at Unique had a nuchal scan at 12 weeks that suggested an increased risk of Down's syndrome. However, this risk was shown to be slightly decreased at an 18 week scan and no other anomalies were found. Another mother had low fetal movement in the last month of pregnancy, which resulted in regular monitoring at hospital (Unique).

Newborn

Newborns with 8p23.1 duplication syndrome may not have any signs or symptoms. However, there may be some physical signs early on. Around half of the babies had a heart defect which was diagnosed at or soon after birth (see page 8). Two babies had trouble maintaining their temperature after birth. One baby had seizures at birth. One Unique baby was floppy and lethargic. Birthweights recorded at Unique and in published medical literature all show a normal birth weight, with an average of 3.37 kilos (7lb 7oz) (Barber 2008; Unique).

Feeding and growth

Feeding difficulties do not appear to be common. However, the hypotonia (floppiness or low muscle tone) that has been described in some Unique babies with 8p23.1 duplication syndrome can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Three babies out of sixteen had a cleft palate (an opening in the roof of the mouth), which affects sucking and swallowing. A number of babies (3/16) have a high palate, which can mean the action of sucking and swallowing is difficult (Barber 2008; Unique).

The hypotonia can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). Two children surveyed by Unique had GO reflux but this has not been reported in published medical literature. GO reflux 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 (Unique).

Growth appears to be normal (Barber 2005; Barber 2008; Barber 2010; Unique).

❝ She was slow to feed after initial post-birth feed and appeared too tired. She was syringe-fed a couple of feeds and then there were no issues ❞ *2 years*

❝ She's a great eater and loves food ❞ *7 years*

❝ He had low muscle tone in his face and a high arched palate but as he has grown older he has a healthy appetite. He eats very well except he has a hard time chewing meats and tough textures. He tends to push food out with his tongue. Although he eats a well balanced diet he is underweight and slim and petite in stature ❞ *7 years*

Appearance

Most children with 8p23.1 duplication syndrome look little different from other children and may closely resemble their siblings or parents. However, others may have facial features in common with other children with 8p23.1 duplication syndrome. They often have a prominent forehead and arched eyebrows. Two children have large heads (macrocephaly) (Barber 2005; Barber 2008; Unique).

❝ She looks essentially 'normal'. Genetic counsellors have noted that she has a prominent forehead with a slight 'mound' in the centre, and arched eyebrows. However, none of these create an 'abnormal' appearance ❞ *2 years*

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

Gross motor skills can be affected and this means that it may take a little longer for children to roll over, sit, crawl and walk. From the limited information available, sitting unaided was mastered between 9 months and three years (average 21 months). One girl is walking around the furniture at 15 months and a boy walked independently at 18 months. Another boy crawled at 2 years and 3 months and walked independently at 4 years. A 7-year-old girl has crawled from 2½ years and has just mastered walking but needs assistance to make sure she doesn't fall down. One boy has not mastered independent walking at seven years but he can cruise around the furniture and uses crawling as his main mode of transport. Children may need considerable support while learning to walk and many children use a stander (a piece of equipment that allows a child to practise standing), a walker and many children benefit from ongoing physiotherapy (Barber 2008; Unique).

22 months

These delays may be attributed to hypotonia that affects some children with 8p23.1 duplication syndrome (Unique).

“ She cannot sit up from supine/prone unaided and cannot stand without assistance. She takes very little weight on her arms when in crawling position. She rolls and reaches to move around in all situations. She is capable of sitting at a table in a chair but often will lose balance if unsupervised. She has a foam wedge to assist her to sit from supine/prone position and a small ladder-like item in order to pull herself up to standing. She also has a gym ball type item (elongated not round) to assist the use of her arms by rolling her forward to the ground and assist her balance. She also has small step stools for sitting on (they are a better height for her) ” *2 years*

“ She learned to walk after aqua (pool) therapy in a zero entry pool. A gait trainer was also helpful ” *7 years*

“ He sits unassisted, with only his hands down to support himself. He crawls and can stand while holding on to something and can walk with support of his upper body ” *7 years*

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

Hypotonia can also affect fine motor skills in children with 8p23.1 duplication syndrome and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles and cutting up food have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard or touch screen computer can often be easier. Toilet training is also likely to be affected (Unique).

“ She does not feed herself with cutlery although she will occasionally take hold of a fork, but she usually takes food off the fork and finger feeds. She is still not good at holding a handled sippy cup and was about 17 months before she made proper attempts to do so. She will pass food and toys from one hand to the other. She will clap but generally not when requested, apparently randomly. She has difficulty letting go of items and does not hand items to people. We are attempting to use a game of dropping noisy spoons into a saucepan to assist in letting go of things. She resists having her hair and teeth brushed ” *2 years*

“ She can dress herself without needing any help ” *7 years*

“ He will find ways to do things for himself, like holding a bottle. He will hold a spoon but does not properly use it. He needs a lot of hand-over-hand help. He can feed himself with his hands. He uses a button to push to operate toys ” *7 years*

Speech and communication

Almost all those with 8p23.1 duplication syndrome described so far have a delay in language skills although there is huge variability. Five children have acquired speech: a 15-month-old has a few words; a 7-year-old has speech and has had speech therapy since the age of 4 years; another child acquired a few words at the age of 5 and will copy some words that are said to him; an 8-year-old has mild language delay and a 15-year-old has a speech impairment (dysathrophonia: an articulation problem that results in growling speech) (Barber 2005; Barber 2008; Barber 2010; Unique).

A 2-year-old has no speech yet but babbles and sings. Her parents have started using sign language and a picture exchange communication system (PECS) to help her

communicate and make choices. A 7-year-old child has no speech but from the age of 5 has used a few signs and also uses PECS. Many children have ongoing speech therapy (Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. Those with hearing loss (see page 8) or a high palate may also have specific difficulty with perceiving and producing certain sounds.

“ She babbles but does not use words and does not apparently babble for communication. She does kick her feet and hit hands on the table when she is excited. She is beginning to use a picture choice to communicate an activity choice in intervention group sessions. The most success has come from mother or grandmother asking questions like, ‘where is Nanny/Mummy?’ and her responding by patting appropriate person’s hand/arm. Also there has been occasional success using this method to show a designated toy or part of body (e.g. hand or foot) ” *2 years*

“ She can sign ‘more’ and ‘all done’. She also looks at the things she wants and will smack her lips for food or a drink. She also has a Panasonic Toughbook™ [a durable laptop] with Boardmaker™ [software for creating picture-based communication] ” *7 years*

“ He has picture cards for language and choice making. He also uses pushing and pulling and has some vocal noises which we recognise – mostly when tired and hungry. We are beginning to use PECS and signing ” *7 years*

Learning

Learning difficulties seem to be a common finding in children with 8p23.1 duplication syndrome. Learning difficulties have been described in 5/11 children in the medical literature and in four children at Unique. Two children described in the medical literature are still babies and so any learning difficulties have not yet become apparent. One child who was diagnosed prenatally is developing normally at 15 months. A 4-year-old also has no learning difficulties. A 4½-year-old has a profound learning disability. A 7-year-old has learning difficulties but reads school books and can write. An adult has learning difficulties but gained five ‘O’ levels at school.

A child with a learning difficulty is likely to need some learning support and many children benefit from attending a special educational school. Repetition and 1:1 assistance are reported by parents to help children learn (Barber 2005; Barber 2008; Barber 2010; Unique).

“ She is predicted to have moderate learning difficulties. She shows strength in music and rhythm and has music therapy ” *2 years*

“ She has a learning difficulty but has learned to read at 4 – 5 years and is in mainstream school with 1:1 help ” *7 years*

“ He is in special educational needs school and in a class mostly learning basic skills like name recognition and early stages of learning. He receives art, music and reading class and everything is assisted. He does well in a sensory-based and play atmosphere ” *7 years*

Medical concerns

Heart

Heart problems have been reported in some (9/16) people with 8p23.1 duplication syndrome. Two children had a hole in one of the walls of the heart. Small holes may close spontaneously; a larger hole usually needs surgical repair. One child has Tetralogy of Fallot, which is a complex heart condition involving both a hole in the heart and an obstruction just below the valve in the artery that leads to the lungs. Blue (deoxygenated) blood cannot easily get to the lungs to pick up oxygen and some of it flows through the hole into the other pumping chamber from where it is pumped around the body. The majority of babies with Tetralogy of Fallot successfully undergo surgery in the first year of life. One child has mild pulmonary stenosis (a narrowing of the pulmonary valve—a flap -like structure that allows blood to flow in one direction, meaning that the heart has to work harder to pump blood which results in breathlessness). One Unique child has a possible small abnormality of the tricuspid valve (a flap-like structure that allows blood to flow in one direction) but no treatment has been necessary (Barber 2005; Barber 2008; Barber 2010; Unique).

Hands and feet

Children and adults with 8p23.1 duplication syndrome may have hands and feet that are not perfectly formed. One child has hands with long fingers and unusually positioned, broad thumbs. A mother and her son both have toes that are partially fused (syndactyly). Two children have unusually small feet and one has large big toes (Barber 2008; Unique).

Digestive system

One problem is constipation, which affects three Unique children with 8p23.1 duplication syndrome. Dietary changes and/or medication can help to manage the problem (Unique).

Two Unique children also had periods of loose stools or diarrhoea (Unique).

Palate

Three children had a cleft palate. A cleft palate can be corrected surgically. A few children have been reported to have a high palate. A cleft or high palate can contribute to the early feeding difficulties seen in children (Barber 2008; Unique).

Vision

One child at Unique has strabismus (a squint). Another child has an eye disorder in that when she looks sharply to the side, one of her eyeballs shifts upwards (nystagmus) (Unique).

Hearing

Some children with 8p23.1 duplication syndrome have a hearing impairment. The most common is a conductive hearing loss caused by fluid in the middle ear (glue ear). Glue ear usually resolves as children get older, secondary to growth and an improving immune system. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, if glue ear persists, many children will need a grommet (a small ventilation tube) inserted into the eardrum. Permanent sensori-neural hearing loss has also been reported in one adult in the published medical literature who also has exotoses (benign lumps in the ear) (Barber 2010; Unique).

Skin

Two Unique children with 8p23.1 duplication syndrome have eczema and two have dry skin with occasional rashes (Unique).

Other

One child had a disorder of her adrenal glands (triangular-shaped glands located on the top of both kidneys, responsible for the release of some hormones). She was treated with adrenal hormone replacement therapy. However, her mother (who also carries the duplication) does not have an adrenal anomaly. One Unique child is due to have adrenal gland testing (Barber 2008; Unique).

One Unique child has a difference in the length of his legs (Unique).

Behaviour

In general, children with 8p23.1 duplication syndrome are happy, affectionate and sociable. However, they are as vulnerable to frustration as other children with a communication disorder. One child is orally fixated on things and mouths everything. He is quite introverted and has been diagnosed with autism and has a high pain threshold. One child described in the medical literature had difficulties with concentration, perception and response and sensitivity to noise. Another child is described as having social and emotional difficulties (Barber 2005; Barber 2010; Unique).

“ She loves squishy toys and tactile experiences – when she is painting she loves just to squeeze the paintbrush! She loves children's TV and in the car calms to nursery rhyme CDs. She really loves 1:1 attention from other people and loves faces – grabbing them and hair! She enjoys touching and watching animals, particularly dogs and rabbits. She enjoys the wind in her face; watching trees move and spinning rides in the playground. She loves playing with her brother ” *2 years*

“ She is always happy and loves everyone. She LOVES water and music. She also loves computers and anything that makes a noise ” *7 years*

6 years

“ He likes to be alone and will often separate himself from other people. He is orally fixated on things and he chews his shirt collar, bibs and a chewy. He likes to watch people, for example looking out of the window or watching his brother. He loves playing with door hinges, swinging doors open and shut. He very rarely cries and has an unusually high pain tolerance ” *7 years*

Sleep

Most children with 8p23.1 duplication syndrome have no trouble going to sleep and staying asleep. However, sleep problems affect some children. Three Unique children do not sleep well. One child has improved as she has grown up and occasionally takes

melatonin. Another Unique child's parents have employed a sleep routine, which has resulted in improvement of sleep and she now sleeps soundly through the night (Unique).

" Sleep was difficult but new sleep management routines have fixed the night-time issues; daytime is still a little challenging in its inconsistency " *2 years*

" She has no sleep problems " *7 years*

" He has spells of not sleeping. He does not settle down and will stay up all night. He will not take naps. We use melatonin to settle him and he will go to sleep " *7 years*

Puberty and fertility

Due to the small numbers of people so far reported with 8p23.1 duplication syndrome, there is no information on puberty. Since we know that two mothers and one father have passed the duplication on to their children fertility is presumed to be normal (Barber 2005; Unique).

Adults with 8p23.1 duplication syndrome

Three adults have been described in medical literature and Unique has one adult member with the duplication.

One mother who passed the duplication on to her daughter had mild facial features and learning difficulties but obtained 5 'O' levels at school and is in employment (Barber 2008).

Another mother who passed the duplication on to her son also had mild facial features, was born with a cleft palate and has had surgery to bring her jaw forward. She lives independently but has support from her family (Barber 2008). However, this mother and child also have a small deletion of the long arm of chromosome 8, which means some of their problems are more severe.

A father who passed the duplication on has a hearing loss in both ears and has learning difficulties (Barber 2010).

If one person in a family with the 8p23.1 duplication is mildly affected, will others in the same family also be mildly affected?

Not necessarily. There is a lot of variation between different members of the same family who have the same duplication. We know that if one person is mildly affected or unaffected, others may be more severely and obviously affected (Barber 2010).

Ongoing research involving 8p23.1

The features of 8p23.1 duplication syndrome are likely to be a result of the extra copies of one or more genes found in this region. Determining the exact size of the duplication is necessary for identifying critical regions and genes that may contribute to the features of 8p23.1 duplications.

The GATA4 gene is believed to be responsible for the heart problems that are common in those with 8p23.1 duplication syndrome. SOX7 has been suggested to play a role in the developmental delay (Paez 2008) and as an additional factor for the heart problems (Wat 2009).

The *TNKS* gene has been suggested to have a role in the behavioural problems that affect some children.

It is important to remember that while identifying the gene(s) responsible for certain features of the 8p23.1 duplication syndrome is valuable and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is extra, it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often 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 how the 8p23.1 duplication occurred. At least four parents are known to have passed the duplication on to their child. However, in most cases the duplication occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 8p23.1 duplications are caused by a change that occurred when the parents' sperm or egg cells were formed, or possibly during formation and copying of the early cells after the egg and sperm had joined.

Whether the duplication is inherited or *de novo*, as a parent there is nothing you did to cause the 8p23.1 duplication and nothing you could have done would have prevented it from occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault.

Can it happen again?

In families where both parents have been tested and have normal chromosomes, the possibility of having another child with an 8p23.1 duplication is almost certainly no higher than anyone else's. One very rare situation that can occasionally occur is that both parents themselves have normal chromosomes by a blood test, but some of their egg or sperm cells are normal while others carry the 8p23.1 duplication. Geneticists call this germline mosaicism and it means that parents whose chromosomes are normal when their blood is tested can have more than one child with the duplication. However, this rare possibility has not yet been found in the parents of children with 8p23.1 duplication syndrome.

If either parent has a chromosome rearrangement or duplication involving 8p23.1 by a blood test, the possibility is greatly increased of having other affected pregnancies. In each pregnancy, someone with the duplication is likely to have a 50 per cent risk of passing it on and a 50 per cent chance of having a child with normal chromosomes 8 without the duplication. Their ability to look after a child is very likely to be closely related to their own degree of learning difficulty.

Parents should have the opportunity to meet a genetic counsellor to discuss their 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

Understanding chromosome disorders
Unique

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This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by Unique and reviewed by Dr John Barber, University of Southampton, UK and by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK and chief medical advisor to Unique.
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