Isochromosome 8p: mosaic tetrasomy 8p

People with this rare chromosome disorder have a small extra chromosome - called an isochromosome - in some cells of the body. The isochromosome consists of two copies of most or all of the short (p) arm of chromosome 8. In these cells there are four copies of the short arm of chromosome 8 instead of the usual number of two. Geneticists call a condition where there are four copies of part of a chromosome a tetrasomy. Having an isochromosome 8p causes a disorder known as mosaic tetrasomy 8p. The effects of this disorder are caused by the genes on the extra chromosome.

Mosaic tetrasomy 8p is very rare: since the first case was reported in 1988, only a total of 17 cases have been reported in the medical literature. *Unique* has three members with this disorder.

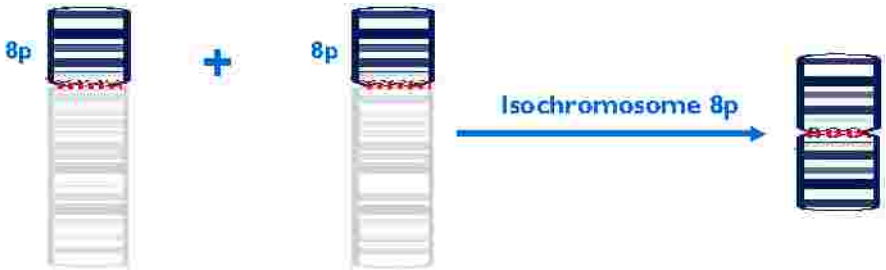
When there are very few cases, with reports only of babies or young children, it's not possible to be certain about the full range of effects of a particular chromosome disorder. In particular, in a mosaic form of a disorder, effects can range from very minor to extremely severe.

But some possible effects of mosaic tetrasomy 8p have been seen repeatedly. Some of these features are also seen in people with mosaic trisomy 8 (where some cells contain a single copy of the whole of chromosome 8).

These features are:

- A degree of developmental delay. The typical range is from moderate to severe. Speech and language appear to be specifically affected
- Structural anomalies of the brain. These typically include agenesis of the corpus callosum (absence of the band of nerve fibres that links the two hemispheres of the brain). They also include enlargement of the fluid-filled spaces within the brain
- Heart problems. These may be simple, such as a hole between the two upper or lower heart chambers, or more complex, involving a number of defects. Children may outgrow some small defects and others are correctable by surgery but this may not be possible for all
- Fused or oddly formed bones in the spine (vertebrae); extra or missing ribs
- Spinal curvature

(Kristoffersson 1988; Robinow 1989; Roskes 1990; Fisher 1993; Newton 1993; Tilstra 1993; Digilio 1994; Schrander-Stumpel 1994; James1995; Winters 1995; Napoleone 1997; Le Bris 2003; López-Pajares 2003; Nucaro 2006; *Unique*)



Chromosomes containing only genetically active material from the short arm beyond band 8p11.22

Of the eleven cases reported in the medical literature, each almost certainly has a different precise breakpoint in the short arm. Many of the reports are also quite incomplete and this limits what can be said about the general effects of an extra chromosome consisting of material from the short arm of chromosome 8 (Ohashi 1994; Batanian 2000; Anderlid 2001; Voullaire 2001; Daniel 2003; Demori 2004; Herry 2004; De Pater 2005).

The **development** of some children with a small extra chromosome between the tip of the short arm and band 8p22 was not affected or only affected in a very slight way. One baby with a chromosome made up of two copies of material from the tip of the short arm to band 8p22 was developmentally ahead of her chromosomally normal brother. A baby with a smaller extra chromosome to band 8p23 was developing normally at two years (Herry 2004; De Pater 2005).

But others with similar extra chromosomes were developmentally affected. A 21-year-old with a ring consisting of most of the short arm of chromosome 8 was judged to have some learning difficulties, with an IQ of 80-85 (Daniel 2003). One 8-year-old child with an extra chromosome as far as 8p23.1 was developmentally delayed but 'good at sports'; a 13-year-old with an extra chromosome as far as 8p23.11 had below average learning abilities and an IQ of 75 (Voullaire 2001). And a 2-year-old with an extra chromosome as far as 8p23.1 had a developmental quotient of 73.

Where the extra chromosome consisted of material from the centre of the short arm between 8p10 and 8p23.1, one child was sitting and moving just within normal developmental limits and at three years was assessed developmentally to be at a 25-month level. In terms of speech, he was a slow starter but putting words together at 3 years (Demori 2004). A child with an extra chromosome made up of material

from between the centromere and bands 8p12 was developmentally normal in his pre-school year but lagged a year behind academically by age 5 (Batanian 2000). A two-year-old with an extra chromosome as far as 8p10 was 10 months delayed at the age of two and had a mild learning disability at 8 (Anderlid 2001).

In terms of **behaviour** and **social ability**, one boy showed autistic-like behaviour at three years of age, with stereotyped conduct, avoiding gaze and repetitive language sounds (Demori 2004). Another boy had unspecified behaviour problems at the age of three (Anderlid 2001), a third was treated for attention deficit hyperactivity disorder at the age of nine and had continuing behaviour problems at 13 (Voullaire 2001) while a fourth was treated for attention deficit disorder with methylphenidate (Ritalin) and imipramine when he was five. He was also on anti-epileptic medication for seizures (Batanian 2000).

As for **growth** and stature, this is generally not commented on but one adult woman was 159cm (5' 3") tall, a 2-year-old girl was slightly short for her age and a 13-year-old boy was in the shortest three per cent of the population for his age (Ohashi 1994; Voullaire 2001; Daniel 2003). Features that might be noticed at birth were unusual although some babies had subtly atypical facial features and one baby had several large birthmarks on her back (Batanian 2000).

One boy was also born with a very small penis, **undescended testicles** and **hernias** in the groin. 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. Inguinal hernias also usually need surgical repair (Voullaire 2001).

Six of the children appear to have enjoyed generally good health while four had significant illness.

Two boys had repeated respiratory infections in the first year of life, in one case as well as asthma and a milk allergy. Both had a significant **heart condition**, persistent ductus arteriosus (PDA), in which a channel taking blood to the lungs during fetal life fails to close as usual shortly after birth. In both cases the channel was surgically closed in the second year of life (Ohashi 1994; Voullaire 2001). A third baby had a heart defect known as total anomalous pulmonary venous return, in which the vessels that bring oxygen-rich blood back to the heart from the lungs are incorrectly connected. Treatment depends on the baby's condition but can include medication to help the heart and lungs work more efficiently and surgery to reconnect the blood vessels. At the age of five, this child developed thrombocytopaenia, where the number of platelets in the blood is reduced, leading to bleeding into the skin, spontaneous bruising and lengthy bleeding (Batanian 2000).

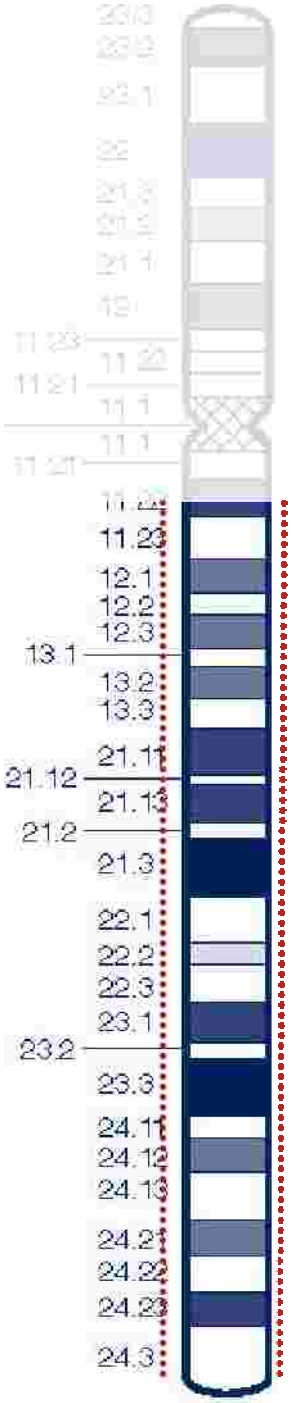
As for other conditions, one baby was noted during pregnancy to have enlarged fluid-filled ventricles within the brain and this was confirmed as hydrocephalus at birth (Batanian 2000). **Puberty** was precocious in one girl, starting at the early age of seven, while a boy in whom puberty was delayed required hormonal stimulus (Batanian 2000; Voullaire 2001).

Extra chromosomes containing genetically active material from the long arm distal from 8q11.22

At least seven cases of rings and markers are listed on http://www.med.uni-jena.de/fish/sSMC/08.htm. Here two cases are described from the medical literature. The extra chromosome material is quite different in each case. So it isn't possible to draw any general conclusions.

An 8-year-old girl with a ring chromosome made up of material from the centromere to band 8q21.1 had experienced some developmental delay, sitting and walking quite late, although this was partly explained by repeated operations to correct her club feet. Her fine motor skills – hand use and coordination – were on track and intelligence-wise, she was about a year behind her peers at school. All the same, she was much stronger in some aspects of learning than in others. Her chief difficulties were social and communicating, not least because she had hearing loss and used sign language. Physically, she was healthy. She had narrow shoulders and subtly unusual facial features that were less obvious than when she was a baby (Anderlid 2001).

A 16-year-old girl with an extra chromosome made up of two copies of the material from the tip of the long arm to band 8q23.3 was born prematurely at 32 weeks and initially tube-fed. As a newborn baby she showed one or two unusual features, including bent fifth fingers, a curved sole on the feet and increased muscle tension (hypertonia), reducing the ability of muscle to stretch. Her fists were clenched and she couldn't fully open her elbows, knees or hips. This feature remained so that as a teenager she couldn't fully open her fingers. She remained in the smallest five per cent of the population for her age. In terms of development, she showed global delay, walking at 18 months and with an IQ of 45-50, suggesting moderate learning disabilities. When she was almost 11, she knew her colours and the alphabet. By 15, she could count to 27 and could undress, but couldn't read and needed help with dressing. Behaviour-wise, she was sociable and affectionate but teachers described her as hard to handle and having only a short attention span. Her increased muscle tone remained and she walked on her toes. Subsequently her ovaries were found to be abnormal (they contained multiple cysts) and she grew some facial hair. She later developed the autoimmune disorder myasthenia gravis, a nerve condition that leaves the muscles around the body weakened (Reddy 2000).



Extra chromosomes of unknown extent

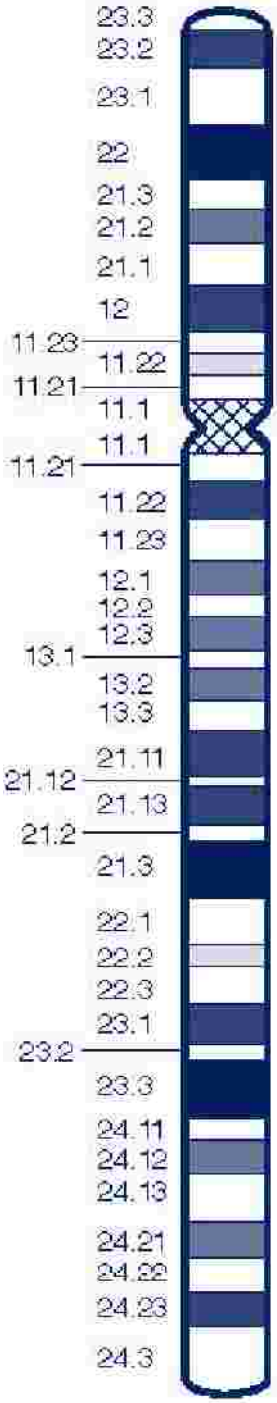
Seventeen people have been reported in the medical literature with an extra chromosome, frequently a ring chromosome, made up of material from chromosome 8 but with no specification of break points, leaving it uncertain what material it contains. Two of them, including a 31-year-old woman, have apparently entirely normal development and were discovered by chance or during routine screening. The comments below do not relate to these two (Plattner 1993; Daniel 1994; Butler 1995; Gravholt 1995; Hastings 1999; Tonk 2000; Daniel 2003; Yilmaz 2005). Nine *Unique* members aged from 6 to 37 years have a similar extra chromosome 8, again usually a ring chromosome.

In terms of **development**, all have shown some delay but the extent is very variable. Some babies have low muscle tone and are late to acquire head control and to roll over. Babies learned to sit alone between seven and 16 months and to walk between 14 months and four years, in some cases initially using a walking frame. Three babies were born with talipes (club foot) requiring casting and sometimes surgery to acquire a normal walking position and in these children walking was understandably delayed. Others were born with more minor effects, such as mild clawing of the toes. Once on their feet, some children have remained unbalanced and prone to tumbles while others move around entirely normally. One adult of 29 years has developed arthritis-like pain in his knees while moving around.

As far as **fine motor skills** are concerned, some are unaffected, while unbending fingers and limited joint movements in the hands and arms make for dexterity problems for others. **Speech** is generally delayed but understanding is usually more competent than expression. Four of the nine *Unique* children had a temporary or permanent hearing impairment with obvious impact on their speech development. Despite this, some children are communicating with words as well as gestures, vocal noises, facial expressions and objects of reference by their third year, while speech emerges in others somewhat later.

" He communicates with signing, pushing, pulling, gestures and vocal noises and now says Mum and Dad - *6 years*

" At the age of three he would say a few words. Now he uses two or three sentences of two words but he still has a problem expressing himself and maintaining a conversation. He understands well, although on occasion it is impossible to make certain situations understood - *28 years*



Children do typically need **learning** support at school, with their abilities ranging from mildly to severely impaired, with many in the moderate range of ability. Typically, children will require a statement of special educational need and will either attend a mainstream school with support or a special school better adapted to their particular needs. Some children learn to read and write but this is not possible for all. Many children have difficulties with concentration and attention as well as a communication deficit that is reminiscent of autism and undermines their ability to learn efficiently until they are correctly diagnosed and appropriately managed.

" He enjoys music and drawing, is good at puzzles, and loves to take things like old radios apart. He likes to fix things and at times is helpful which makes him very happy. He is very slow but likes to do things well even if it takes all day or more - *28 years*

In terms of **behaviour**, children are generally described as well behaved but prone to frustration (angry, impatient, cross, challenging) when they can't communicate what they want or get their own way. Autistic tendencies may undermine social skills but this is not universal and some youngsters are easy-going and well-liked.

" He can be very calm and well-behaved but also very demanding with tantrums if he doesn't get his own way. He likes to be with other children and to be cuddled. He's strong-willed: when he wants something he doesn't give up until he gets it - *6 years*

" Most of the time he is a very peaceful person but there are days where he gets angry easily but this has never been a problem. He's a little shy socialising in the beginning but when he feels comfortable he enjoys the company of others. He is well liked by everyone. He's very special with us, his parents, when we are sick. He worries a lot and takes good care of us. He loves to buy me things and knows just what I like because he goes everywhere with me - *28 years*

In terms of **growth**, information is available on six people, only one of whom was short for his age. All others were of normal height or unusually tall with a slender build. **Facially** the one feature of note is large ears which in one child were corrected with plastic surgery to give them a more normal appearance.

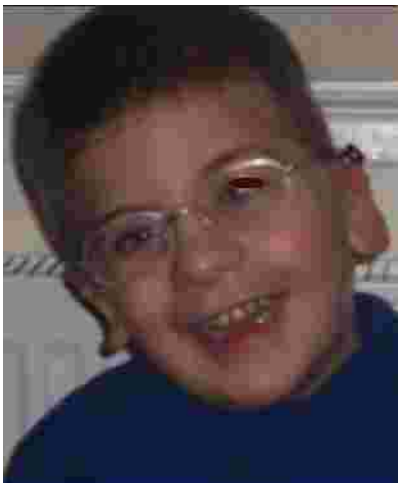
There is little information on **feeding** and it seems that some babies at least will breast feed without particular difficulties and move on to thicker feeds and solid foods at an appropriate age. Others will need support with feeding and may thrive better when fed from a bottle. Reflux, where feeds return up the food passage and may be vomited, has occurred in some children and will need careful management with appropriate seating positions and possibly thickened feeds and prescribed medication to help prevent feeds from returning up the food passage. Children may be late to wean on to solid foods and need them puréed or finely chopped for much longer than other children.

In terms of **general health**, one 15-year-old developed **seizures**, but they responded to medication, which was then stopped after two years. One child was diagnosed with leukaemia. One baby was born with a hole between the two lower (pumping) chambers of the **heart** and this was successfully repaired surgically. Four children had some degree of kidney involvement: one had a small, non-functioning **kidney** removed; another had an arrangement known as horseshoe kidney, where the bottom points of the two usually separate kidneys are joined, creating a U (horseshoe) shape; another child had the ureters that lead from the kidneys to the bladder surgically reinserted;

another young child with a swollen kidney (hydronephrosis) took low-dose antibiotics to protect his kidneys. Minor **genital** anomalies are not uncommon in children with a rare chromosome disorder and this was true of four children with a small extra chromosome 8: one boy was born with hypospadias, where the hole normally at the end of the penis is on the underside instead; another had unusually small testicles, with one not fully descended into the scrotum; another had a very small opening for urine, corrected surgically; and one girl was born without a clitoris. A developing spinal curve is a feature of the condition known as trisomy 8 mosaicism and is seen in people with an extra part of chromosome 8: the curve may be sideways or forwards and can be slight, needing no more than monitoring or more severe, needing bracing or even surgery.

Eyesight is affected in six of the *Unique* members, although problems are varied, including glaucoma (a rise in the internal pressure within the eye), a squint (strabismus), short sight and Duane's syndrome (restricted turn of the eye). Three members have a degree of loss of vision but this is not so severe in any as to need special teaching.

How did the extra chromosome come about?



Some small supernumerary chromosomes are inherited. The mother or the father has the same small chromosome. A blood test to check the parents' chromosomes will usually show if this is the case.

But most small extra chromosomes occur in children both of whose parents have normal chromosomes. Geneticists call this de novo (dn), meaning that this has occurred as a new event. These extra chromosomes are caused by a change that occurred when the parents' sperm or egg cells were formed or around the time of conception.

There is still quite a lot of uncertainty about the events that caused the small extra chromosome to form. But what is known is that as a parent you cannot change or control them. Children from all parts of the world and from all types of background have small extra chromosomes. No environmental, dietary or lifestyle factors are known to cause them. There is nothing that either parent did before or during pregnancy that can be shown to have caused the extra chromosome to form, and equally nothing could have been done to prevent it.

Can it happen in another pregnancy?

When the parents' chromosomes are examined they are usually found to be normal. Where both parents have normal chromosomes, it is very unlikely that a second child will be born with a supernumerary chromosome 8.

When, as occasionally happens, one parent has a supernumerary chromosome 8 themselves, the chance of passing it on is theoretically as high as 50:50 in each pregnancy, but in reality is somewhat lower.

Unique

Support and Information

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This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by *Unique* and reviewed by Privatdozent Dr Thomas Liehr, Institut für Humangenetik und Anthropologie, University of Jena, Germany and by Professor Maj Hultén, BSc, PhD, MD, FRCPath, Professor of Medical Genetics, University of Warwick, 2009

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