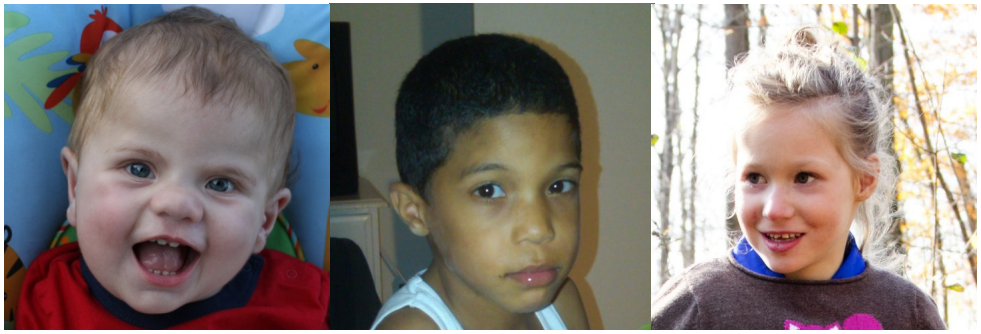
Understanding chromosome disorders

Unique

Trisomy 8 Mosaicism



rarechromo.org

Sources and References

The information in this guide is drawn partly from 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 surveys of members of Unique conducted in 2003-4 and 2011-12, referenced Unique. When this guide was written Unique had over 90 members aged 18 years and under with T8M. Unique also has 29 adult members with T8M. Unique is very grateful to the families who took part in these surveys.

Trisomy 8 Mosaicism

Trisomy 8 mosaicism (T8M) is a chromosome disorder caused by the presence of a complete extra chromosome 8 in some cells of the body. The remaining cells have the usual number of 46 chromosomes, with two copies of chromosome 8 in each cell. Occasionally T8M is called Warkany syndrome after Dr Josef Warkany, the American paediatrician who first identified the condition and its cause in the 1960s. Full trisomy 8 – where all cells have an extra copy of chromosome 8 - is believed to be incompatible with survival, so babies and children in whom an extra chromosome 8 is found are believed to be always mosaic (Berry 1978; Chandley 1980; Jordan 1998; Karadima 1998).

Genes and chromosomes

The human body is made up of trillions of cells. Most of the cells contain a set of around 20,000 different genes; this genetic information tells the body how to develop, grow and function. Genes are carried on structures called chromosomes, which carry the genetic material, or DNA, that makes up our genes.

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 from the largest to the smallest approximately. Each chromosome has a short (p) arm (shown on the left in the diagram below) and a long (q) arm (on page 3). 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.

Chromosome disorders are usually detected by examining cells prepared from a blood sample. However, in T8M there are usually more cells with the extra chromosome 8 in the skin than in blood so a skin sample may also be taken. A number of cells will be analysed and a report prepared, giving the karyotype: a chromosome description. This will usually state in brackets the numbers of normal and trisomic cells. A karyotype for a boy with trisomy 8 mosaicism might look like this:

47,XY,+8[28]/46,XY[22]

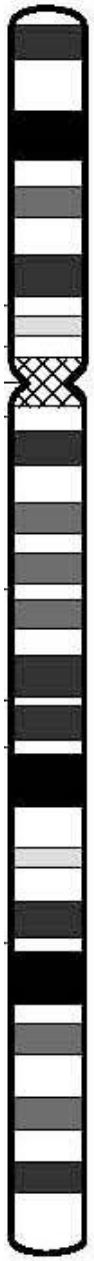
This means that of 50 cells tested, 22 had the usual number of 46 chromosomes, while 28 had an extra chromosome 8. Your geneticist or the laboratory that identifies the presence of T8M should be able to tell you what proportion of your child's cells have 46 chromosomes and what proportion have an extra chromosome 8. This will not give an indication, however, of whether T8M will affect your child mildly, severely or not at all.

Main features

The features of T8M are extremely variable. One mother had identical (monozygotic) twins, each with T8M but showing quite different effects of the extra chromosome. Descriptions in medical journals have nonetheless allowed a 'typical' picture of T8M to emerge (Webb 1998). The experience of Unique families has confirmed this outline and helped to colour it in, but each person with T8M has an individual pattern of features, problems and talents. In any child some, but not all, of the 'typical' features listed will be recognisable.

- **Build**
  Babies are born with a normal weight and length. They may have a short neck, occasionally with extra skin folds, and a long slim body with a narrow chest, shoulders and pelvis, which may become more apparent with age.
- **Limbs**
  Stiff joints with a limited range of movement; clenched or bent fingers and/or toes; deep palm and sole creases; occasionally underdeveloped nails; missing or small kneecaps (termed 'patellae').
- **Facial appearance**
  A pear-shaped, bulbous nose with upturned nostrils, a protruding lower lip and large ears.
- **Medical problems** include kidney and urinary conditions; congenital heart conditions, many healing spontaneously; absent or underdeveloped band of nerve fibres linking the two hemispheres of the brain (corpus callosum); vertebrae and other bones may be fused together.
- **Effect on learning and speech**
  A few people appear unaffected by T8M, while others typically have mild to moderate intellectual disabilities. Speech is usually disproportionately delayed but in some children verbal ability exceeds performance ability.

Chromosome 8



How common is T8M?

T8M appears to be rare, affecting only one in every 25,000 to 50,000 babies. It is known to affect boys more often than girls (at a sex ratio of 4:1) although the reasons for this are not yet clear. More than 120 people with T8M have been described in medical journals. Currently over 100 families affected by T8M are members of Unique and have long-term experience of living with this chromosome disorder (Gorlin 1990; Wisniewska 2002; Hale 2009; Unique).

Are there people with T8M who have developed normally and have no speech, learning or health difficulties?

Yes, there are. The features of T8M are extremely variable. Some people appear unaffected, either physically or developmentally. One is a college professor. People who are unaffected are only diagnosed if they have another relevant medical concern, such as a fertility problem (Reyes 1978; Camurri 1991).

What is the outlook?

There appears to be no reason why people who are healthy should not enjoy a normal lifespan. The growing number of incidental reports of T8M discovered during investigation of another medical problem shows that many people with this chromosome condition lead independent adult lives. It becomes easier to predict the future for any individual once their abilities and strengths have revealed themselves. Many adults have been described in the medical literature and Unique has 29 adult members. Unique has also produced a guide to Adults with Trisomy 8 mosaicism (which can be downloaded from the Unique website: www.rarechromo.org).

Pregnancy

Most mothers carrying babies with T8M experienced no pregnancy problems, had a normal delivery, and only discovered their baby was affected after the birth. However, prenatal ultrasound scans revealed anomalies in a few babies. Four babies had enlarged kidneys (hydronephrosis) identified on a prenatal ultrasound. One of these babies also had a fetal MRI which identified agenesis of the corpus callosum (ACC: a brain anomaly; see page 13). Another baby had ACC detected at 28 weeks. Another baby was seen to have hydrocephalus (excessive fluid on the brain) on a 28 week ultrasound scan and a subsequent amniocentesis showed the presence of T8M. One mother, pregnant with twins, had a result from the nuchal fold scan which was suggestive of an increased risk for Down syndrome. Subsequent chorionic villus sampling was negative for Down syndrome but as T8M was not looked for, it was not diagnosed (Unique).

One mother had an increased amount of alphafetoprotein (AFP) in a maternal screening test while pregnant. This test can indicate the presence of a chromosome disorder;

however, the mother chose not to have an amniocentesis. Two mothers had bleeding during pregnancy and one had polyhydramnios (an unusually high volume of amniotic fluid), which resulted in her being induced at 38½ weeks (Unique).

At least six babies were born prematurely (at less than 37 weeks) (Unique).

More information about detecting T8M in pregnancy can be found on page 17 of this guide.

Feeding and growth

Some babies with trisomy 8 mosaicism will have difficulty feeding but this is not universal. Feeding problems are common in children with chromosome disorders and Unique has a wealth of specific advice. Weak, unco-ordinated sucking as a newborn baby and gastro-oesophageal (GO) reflux (where the contents of the stomach flush readily back up the food pipe, causing spitting up or vomiting) mean that a high proportion of Unique children were tube fed or had a gastrostomy fitted, to allow feeding directly into the stomach. Swallowing difficulties were common in babyhood and chewing difficulties remained in some older children. Children with a high or cleft palate faced specific difficulties in drinking (Unique).

Growth appears to be normal although growth continues in some people for longer than is typical (Unique).

Will someone with T8M look different from other people?

A typical baby with T8M will look very much like other babies. Any distinctive facial features are quite subtle. Signs that are highly suggestive of the condition, such as deep lengthwise creases in the skin of the soles of the feet and sometimes the palms, are only obvious if you look for them. With time, these may fade or vanish while other signs may become more obvious, such as a long, narrow chest and pelvis and a limited range of movement in some joints. Doctors do describe a typical 'look' to the face of a child with T8M that includes a rounded forehead, rather prominent, cup-shaped ears, deep and wide-spaced eyes, a broad nasal root and a pear-shaped nose, a full mouth with a pouting lower lip and a small jaw (Kosztolanyi 1976; Jordan 1998).

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

There is great individual variation in children's mobility, but typically children reach their developmental milestones a little late. The information at Unique is that babies were rolling over at around 8 months (range 4 months to 2 years); sitting at around 10 months (range 5 months to 3 years); crawling around 16 months (range 9 months to 7 years) and taking first steps around 18 months (range 1 year to 7 years) . Gait may be uneven or on tiptoe as a result of joint and tendon restrictions (see page 11). Some children are described as clumsy and trip over a lot, or have poor co-ordination. A small number of children have uneven leg lengths, part of a picture of asymmetry that is common in mosaicism. Among Unique's members, one 5-year-old was playing tag and was about to join a soccer team; one child is trying to pedal a tricycle at 8 years; one child enjoys kicking a ball about and does gymnastics; a 9-year-old loves playing football but is unco-ordinated and took a long time to learn to catch a ball; an 8-year-old loves gymnastics and swimming and learned to jump on two feet at the age of 7; three people do not walk. Four children needed leg braces. Some adults retained an awkward gait. Most could swim and continue to improve mobility skills in adult life. One member learned to ride a two-wheeler for the first time at the age of 28. The stiff joints that are characteristic of T8M have a pronounced effect on children's mobility (Schinzel 1974; Wisniewska 2002; Unique).

'He is crawling and pulls to stand at everything he can" – 1 year

"He has just started to walk so he is very sure indoors but wants a hand to hold outdoors. He needs help to climb the stairs and when he climbs alone he needs a lot of time. He likes to dance with his sister. The physiotherapist and osteopath have been very important" – 2½ years

"He will walk but not far because he trips a lot. Climbing needs supervision. He loves football" – 4 years

"He had significant delays in his gross motor skills and still has many delays. He is able to play with other kids his age but tires easily and is generally slower and weaker. He can run, jump, climb, throw and catch a ball and ride a tricycle" – 4½ years

"He has no problems – plays, climbs and runs normally" – 4½ years

"He feels pain in his joints and can't walk very far and gets tired very quickly. Because of this he doesn't really enjoy physical activities" – 5½ years

"She never really walks but always skips and runs! She has always enjoyed climbing and loves to dance around and jump, although she is clumsy and falls a lot while trying" – 6 years

"His movement is not as fluid as his peers. He climbs stairs one foot at a time" – 7 years

"He plays football although is very unco-ordinated" – 8 years

"He currently walks and runs without assistance, though is unsteady especially when navigating changes in terrain" – 9 years

"He rides a normal bicycle now. Sport is difficult" – 12 years

"He can walk unaided (but closely supervised) slowly in a familiar environment. Otherwise uses a wheelchair" – 15 years

"He still has poor co-ordination and is clumsy but has improved with age. He is now able to ride a bike. He no longer needs a wheelchair as he manages well now although he soon tires" – 17 years

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

Tightly contracted and bent finger joints limit dexterity, and affect everyday tasks like dressing and school activities like writing. 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. As is typical for T8M, the range of personal care tasks that children can undertake is very wide. Over the age of five, only five Unique youngsters were fully dependent on a carer for washing and dressing. Difficulties with co-ordination, balance and clumsiness did affect most, although only two had a formal diagnosis of dyspraxia. Hydrotherapy, massage and aromatherapy were popular adjuncts to surgery, splinting and regular physiotherapy for tightly contracted joints.

Toilet training is also likely to be affected. The information at Unique is that children are toilet trained around the age of 3½ years (range 2 years to 5 years) (Unique).

"He can reach and grab things and has great grip but his fine motor skills are a little delayed" – 10 months

"He is still in nappies [diapers]" – 4 years

"He has significant fine motor delays and began occupational therapy (OT) at 3 months. His hands are small and weak. He can now make purposeful marks on a paper, trace some letters, draw a face and cut with scissors" – 4½ years

"He is only just out of nappies at age 5 years. He needs help getting dressed and constant help and reminders of what he is doing. He gets sidetracked and these daily things can becomes stressful for him" – 5½ years

"Her joints are very flexible so she has trouble holding a cup and has never been able to do zips or buttons" – 6 years

"He had a delayed pincer grasp. Play therapy at home helped. He is out of nappies in the daytime but still in nappies at night-time and when he is ill" – 7 years

"He could not grasp toys or a bottle as an infant. He still has difficulty with buttons" – 8 years

"He has some fine motor delays, especially bilateral co-ordination. Currently developing handwriting skills (legibility, alignment etc)" – 9 years

"He can care for himself but needs lots of reminders: for example, he doesn't remember to take showers or brush his teeth" – 12 years

"100 per cent dependent for personal care" – 15 years

"He learned to fasten laces last year although finds it awkward to fasten tight. He has a special board for chopping vegetables on which he has to use sat at a table to allow him to control his chopping and be safer on task" – 17 years

Learning

It is not certain how many people with T8M have learning difficulties. Some people with the condition learn at a normal pace while others do not. What is certain is that people with T8M who have learning difficulties are more likely to have been investigated and reported in the medical literature than those who have no learning difficulties. Some children show only a specific learning difficulty such as difficulties with visual scanning and synthesis (Theilgaard 1977; Hummel 1988). Among 42 Unique families, eight children have been assessed as having no learning difficulties, eight have mild difficulties, 14 have moderate difficulties, five severe and seven are unknown or are too young to be assessed. There is a trend towards increasing learning difficulties as children get beyond primary school (Unique).

Four Unique members are noted to have areas of 'savant' or specialist knowledge. Two, both with mild difficulties, lack any concept of time. One shows a disparity between academic knowledge and life skills needed for usual adult functioning (Unique).

Among the individuals with no reported learning difficulties is a 5-year-old with speech delay who scored the maximum achievable on kindergarten tests, another 5-year-old who is currently learning to read and write and is reading the same books as his peers in class; an 8-year-old only experiencing specific

difficulties with writing, speed and problem solving in mathematics, a 9-year-old doing averagely well in a mainstream school and an adult of 31 living independently. Among those facing slight difficulties is an 8-year-old who has delays in reading and writing, and has difficulties with concentration but is more able at maths, computers and music; a 9-year-old performing at an age-appropriate level but more slowly than his classmates; another 9-year-old who is in mainstream school with special classes for some subjects; a 12-year-old who attends mainstream school with some additional help; an adult who "reads college level encyclopaedias but cannot remember to take a bath." Among those with a severe learning difficulty is an 11-year-old who can read individual words and count to 12 and a 20-year-old with a reading age of 7 who passed part of his Duke of Edinburgh bronze award and gained a range of qualifications for specific life skills.

"Computer skills is one area where we have seen him shine" – 4 years

"He has a great memory and is a very persistent learner. His cognitive ability is average for his age but he has difficulty focusing and maintaining attention" – 4½ years

"He is learning to read currently and is reading the same books as his peers in class. He has very strong recall. His determination allows him to achieve anything he sets his mind to" – 4½ years

"If the subject is interesting, his memory is good! He learned to read at the age of 6 and is now drawing at the level of a 4-year-old. He is a visual learner and needs to learn at his own pace" – 7 years

"He has significant developmental delay. His memory is poor but he is more able at maths. He started to read at age 7 and is reading basic reading books" – 8 years

"He has a mild learning disability. His memory is excellent for things he cares about! His more able areas are maths, computers and music. He started reading at the age of 6-7 years. He has an 'artful learning' curriculum at his school which facilitates learning by tying academic subjects to visual and music-based experiences and themes" – 9 years

"He has a great thirst for knowledge. If something interests him, he will ask countless questions" – 10 years

"He began to read and write at age 7 and has a good memory. He needs lots of practice to learn" – 12 years

"He has a moderate learning disability and auditory processing delay. His strengths are music and maths. He learned to read at 8 years and loves drawing but hates writing" – 12 years

"He has achieved 8 grade Cs and 1 grade B in his GCSEs with lots of support. He works best in a calm quiet environment. He is now at college doing a foundation course. He has a good recall memory but if given tasks to do he needs prompting and reminding to complete them. He finds it hard to stay focussed for long periods when working although could sit at a computer playing games for hours! He reads comics and magazines. His writing skills are poor with poor spatial awareness on paper" – 17 years

Speech and communication

Reports in the medical literature suggest that speech is typically disproportionately delayed. However, this is not universal and there are some reports of children with high-level speech abilities (Kosztolyani 1976; Theilgaard 1977; Camurri 1991; Jordan 1998; Agrawal 2011). There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The high arched or cleft palate that affects some children with T8M may mean that children have difficulties with certain sounds (see page 12). Unique families confirm that speech is the most obviously delayed area of development in childhood. Understanding usually advances ahead of speaking and many children have specific problems with articulation. Their speech is typically too unclear to be understood by people outside the family and nearly all supplement their speech with signing and gestures. They rely heavily on a skilled and consistent speech and language therapy service. By the mid-teens, the general picture improves, with more youngsters relying on speech to communicate and half of the adults have no reported speech problems.

"He went on a school trip recently and was entertaining everyone by telling them jokes, making them up as he went along, not always funny which made people laugh even more!"

"His speech can at times be unclear and he gets frustrated. We get around this by asking 'How big?' 'What colour?' or 'Where is it?' to help."

"We do sign language with him and he comprehends it more than he makes the signs. He can sign 'more' and 'all done'. He makes some basic noise but is very quiet" – 18 months

"He has signs and vocal noises and a few words ('water', 'Mum'). Although he can't speak he understands it all. When playing we offer him two pictures of toys and he has to choose which he likes a lot" – 2½ years

"He uses signs and has some words. He doesn't pronounce the last letters and sometimes the first letters of words" – 4 years

"He started to speak at 3 years and used some signs and gestures before that. He now puts 4-5 words together in a sentence and uses many phrases ('what are you doing?' 'I love you too'). He is articulation is still poor" – 4½ years

"He is constantly speaking! His vocabulary is very good but his enunciation is a little bit delayed due to the muscular weakness around his mouth" – 4½ years

"He is verbal but his understanding is very low. He can use 2-3 word sentences but he is extremely quiet and has a lisp. PECS (picture exchange communications system) has been very good and he relies on a PECS timetable when he is upset" – 5½ years

"She is deaf and has a cochlear implant. She has a lot of gestures and little speech but always gets her point across. She is now starting to sign more than one word" – 6 years

"He speaks in proper sentences but omits certain words occasionally. Clarity is an issue. He uses a communication board and uses a laptop for all schoolwork (which has a talking software option)" – 7 years

"He started with signing as a toddler but now he has speech. He can speak in sentences but not very clearly. He has had lots of speech therapy and has most difficulty putting together syllables" – 8 years

"He uses signs and is capable of forming complex sentences. He finds it hard to make the sounds of speech clearly" – 9 years

"He has good speech – a little slow" – 12 years

"He started talking around the age of 2-3 but prior to that he used signs and was very good at signing. He now uses full sentences but has a hard time getting out what he is thinking. Reactions are often delayed and processing speed is slow" – 12 years

"At 15 years old he is not talking" - 15 years

"His speech is sometimes hard to understand but he will repeat himself happily if not understood. 'L' and 'sh' sounds are particularly hard for him to articulate" – 17 years

Medical concerns

The findings are extremely varied. A new baby with a prenatal diagnosis of T8M will be very carefully examined to rule out any physical problems which might need treatment. These investigations should not cause alarm; on the contrary, their purpose is to identify any problems early enough for effective help.

Urinary and kidney conditions

According to reports in the medical literature, around half of all children with T8M have a urinary or kidney condition. This is backed up by the Unique experience: 26 out of 42 individuals were affected (62 per cent). However, apart from the six who required surgery, one in the womb before birth, problems for most other children were mild. Urinary reflux (where urine flushes back from the bladder towards the kidneys) was the most common, usually only requiring regular monitoring and protective antibiotic treatment (Unique).

Heart conditions

One baby in four with T8M is born with a heart condition (Wisniewska 2002). Among the 16 (out of 94) Unique members who have reported a heart condition, only four needed surgery; one for pulmonary stenosis (a narrowing of the valve in the vessel that takes blood from the heart to the lungs); two to close holes in the heart wall; and one for persistent ductus arteriosus (a blood vessel that usually closes shortly after birth stays open, making the lungs receive more blood than they should and making the heart work too hard). All other heart defects healed spontaneously, including several small septal defects – holes in the walls between the left and right chambers of the heart (Unique).

Joints

Stiff and sometimes twisted joints are typical of T8M. Knees, hips, neck, wrists, ankles, elbows and shoulders can be affected and families report that young children swivel from the waist to avoid turning a stiffened neck. Older adolescents and young adults may complain of chronic arthritic pain. Joints may be imperfectly formed; the bones either fused together or, by contrast, hips and knees may not be sufficiently moulded to create a stable working joint, needing splinting and/or surgery and immobilisation. Hands and feet typically have hooked or bent fingers and toes (hammer toes), sometimes with fused bones or an otherwise abnormal bone structure. Splinting, casting and surgery to loosen or lengthen tendons have varying success rates. Unique members reported satisfaction with therapies such as massage and aromatherapy; and with injectable anti-inflammatory medication or 'Botox' (botulinum toxin type A) and TENS machines (transcutaneous electrical nerve stimulation, as in childbirth) for joint pain (Unique).

"He can't put his arms up [above his head] because his shoulders are tight"

Spine

Spinal curvature (scoliosis - a sideways curve or kyphoscoliosis - a combination of a forwards hump and a sideways curve) has been reported in around a quarter of Unique members. Severity ranges from slight (needing no treatment) to severe (needing a body brace or surgery). Two Unique members reported a tethered spinal cord (the spinal cord is abnormally attached to the tissues around the spine) for which surgery to untether the cord was successful (Unique).

One Unique member and a 33-year-old man in the medical literature have been diagnosed with cauda equina syndrome, which is a relatively rare but serious condition that describes extreme pressure and swelling of the nerves at the end of the spinal cord (Hale 2010; Unique).

Genital area

Undescended testes appear to affect some Unique boys with T8M. All have needed surgery and the operations to bring down the testes have all been successful. In one boy, one testis was smaller than usual. Other unusual genital features include hypospadias (where the hole for urine that is usually at the end of the penis is on the underside instead), hydrocele (a fluid accumulation round the testicle in the scrotum) and a small penis (Unique).

Seizures

Seizures are reported to affect around one person in six, usually where there is also a brain malformation. Of the eleven Unique members who are affected by seizures, all but one are controlled with medication. Three only had seizures as small infants and no longer take medication. One had seizures between the ages of 1 and 7 years but they have resolved by the age of 13 years. In four of the eleven children a brain anomaly was also noted. One child had two drop attacks between the ages of 2 and 3 years which were thought to be possible seizures (Datta 2010; Unique).

Tongue tie and fusion

Tongue tie has been observed at a high rate in those with T8M, both at Unique and in the medical literature. Tongue tie can cause problems with breastfeeding and with speech, but does not always do so, and opinions vary about whether and when to treat (by snipping, known as frenulectomy) (Theilgaard 1977; Rauen 2003; Unique).

Palate

A high arched or cleft palate (an opening in the roof of the mouth) that is reported to occur in around half of children with T8M. Velopharyngeal insufficiency (VPI) has been reported, in which the air spaces at the back of the throat do not close off completely due to a cleft or short palate and air escapes through the nose. Children with VPI are especially prone to recurrent middle ear infections and colds. If speech therapy fails to improve nasality, pharyngioplasty (repositioning tissue from the palate and the back of the throat to stop air escaping through the nose) has been shown to be successful (Vantrappen 2002; Agrawal 2011; Unique).

Infections

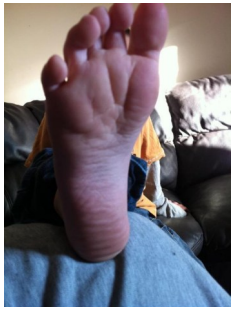
Infections may be more common in children with T8M, making routine immunisations against common childhood infections even more important than for other children. If you have concerns about any immunisations, discuss them with your paediatrician (Unique).

Association with leukaemia

Certain people with T8M have a very slightly increased risk of developing leukaemia or another type of cancer. This specifically affects those people in whom the extra chromosome 8 is found in cells in the blood and who have cells with the extra chromosome in their bone marrow. This association may mean that some adults with T8M need to be monitored by an oncologist or haematologist (Ando 2005; Unique).

Other typical features

These features are typical but need no medical treatment.



Foot and hand creases

Deep creases in the soles of the feet and/or the palms of the hands, together with thickened skin, are one of the most consistent signs of T8M. They affected 33 out of the 42 Unique members surveyed, and in 26 children both hands and feet were deeply creased. The palm creases are usually most obvious in babyhood, and on both hands and feet may vanish as children grow.

Absent corpus callosum (agenesis of the corpus callosum: ACC)

A brain scan may reveal a missing corpus callosum. The corpus callosum is the broad band of nerve fibres that connects the two sides (hemispheres) of the brain. The effects of a missing corpus callosum are usually assessed in the context of any other unusual findings in the brain and how well a child is functioning. This feature was found in more than one quarter of Unique members.

Kneecaps

Typically, one or both kneecaps may be missing or only partly formed. There is no need for treatment.

Hearing

A small number of children have either a temporary hearing loss caused by conductive deafness, usually as a result of glue ear or permanent nerve deafness. In the Unique series 12 out of 58 children had a hearing impairment; two required a hearing aid and one child had a cochlear implant in one ear.

Quite a few children had glue ear: a build-up of fluid in the middle ear. Glue ear usually resolves as children get older and the ear tubes widen and become more vertical, resulting in improved drainage of the middle ear. Therefore, any hearing loss caused by glue ear is usually temporary. However, persistent fluid in the middle ear and glue ear can reduce a child's hearing at a time that is critical for speech and language development. Therefore, while glue ear persists, many children will need a grommet (a small ventilation tube; also known as PE tubes) inserted into the eardrum (Hale 2009; Unique).

Eyesight

Vision problems are common in T8M. Strabismus (a squint) occurs most frequently and can usually be corrected with glasses or surgery. Some babies and children have opaque areas on the cornea (the front of the eyeball) or cataracts, which can be removed surgically. In addition, some children have a coloboma, a developmental defect of the eye which may give a 'keyhole' appearance to the coloured part of the eye. A few children have a loss of vision in one or both eyes, but in Unique's membership no child was registered partially sighted (Scott 1997; Anwar 1998; Unique).

Behaviour

As in other aspects of T8M, the range of different types of behaviour is huge and this broad spectrum suggests that there is no consistent behaviour pattern. Children with T8M may be extremely popular and sociable or just the opposite – shy and lacking in self confidence. Frustration at being unable to communicate potentially causes tantrum behaviour in all children, including those with T8M. Several children under 10 were reported to have severe tantrums, sometimes with head-banging and self harm. By the teen years tantrums appeared to fade, but from the middle teens there were occasional reports of violent and aggressive outbursts. These contrasted with episodes of painful shyness and immaturity, sometimes co-existing in the same youngster. Autistic spectrum disorders (ASD) were mentioned by five families. A diagnosis of autism can be extremely helpful in accessing services and tailoring the educational and behavioural therapy to meet to specific needs of a child with autism. Attention deficit hyperactivity disorder (ADHD), characterised by restlessness and a short attention span, was mentioned by three families (Unique).

"Without being told expectations or limitations, he continues to surprise and amaze me."

"When he is able to achieve at whatever it might be, his face lights up and he is so proud

of himself!"

"He has progressed far beyond what we thought possible. He has a good sense of humour and is very affectionate. The pleasure when he achieves something is priceless. "He has taught me courage and patience. I would not trade him for the world. I am a far better person having him to teach and understand. He has a wonderful sense of humour and has been through 18 surgeries with not one complaint."

"He is a happy, mostly mellow baby" – 10 months

"He loves playing with his 6-year-old brother. He is shy with strangers. He can have severe temper tantrums when he doesn't get his way – 1 year

"He is such a joy and people-person" – 18 months

"When he was younger he was very angry when he found any difficulties but he is very patient now. He likes to play with people and is very loving, giving hugs and kisses" – 2½ years

"His behaviour is very good most of the time but if he doesn't want to do something he will let you know – he screams and rolls on the floor. He is shy around people he doesn't know! – 4 years

"He loves trains, cars, fire trucks and police cars. He loves playing with other children. He is still less mature than his peers and lacks certain social cues. He is usually well-behaved. He often needs prompts and reminders to do tasks. He sometimes gets frustrated when he can't accomplish something on his own or when he is not understood" – 4½ years

"He loves music and dancing. He loves animals and small children and has a very soft nature. He is a very sociable little boy who is confident in trying new activities within new environments. He becomes frustrated when he is unable to do something and we are trying to work with him to ask for help rather than work himself up into a frenzy. He is incredibly loving to his family and friends" – 4½ years

"He does not interact socially with other children but will always seek out adults. He has ASD which was diagnosed at 2 years" – 5½ years

"She loves animals and TV. She prefers to play on her own with other children by her side only. She will ask children to come with her and do what she wants but not much interaction. She loves books but bores easily. She has ADHD and takes medication for it. She also has obsessive compulsive disorder (OCD) and she likes to line things up, sort things in an order that only she knows. If you try to help her she gets very upset and pushes you away. Routine is key. Her smile and loves are so endearing. She has a great imagination" – 6 years

"He loves TV, swimming and anything to do with space! His smallest achievements are major events and celebrated by everyone! He is an inspiration! He is shy and quiet but finds appropriate interaction difficult so becomes aggressive occasionally" – 7 years

"He is very friendly and outgoing. He occasionally (less as he gets older) has severe rages which are completely uncontrollable" – 8 years

"His passions in life are music (bluegrass, jazz) and sports (especially basketball). He can experience challenges with anger management and impulse control. When he loses control he will bite, hit etc. This is at home, usually aimed at parents. Behaviour at school

is not an issue. We are currently consulting twice a month with a behavioural therapist. He is extremely sociable and enjoys being around others and interacting" – 9 years

"He is very sociable and loves playing, watching TV and playing on the computer"- 12 years

"He is overly loving with an extreme innocence that is so sweet. He can be very difficult when forced to do something he does not want to do like homework and chores. He can seem very rude with his abrupt way of saying things. He is very black and white and cannot understand connotations. He doesn't 'read between the lines' and this can cause problems. He has been diagnosed with attention deficit disorder (ADD)" – 12 years

"His strength is his mischievous personality, his sense of the ridiculous along with his infectious laugh and loving nature. He has a high pain threshold and self harms when suffering stomach pain, frustrated, scared or tired. He loves swimming and being outdoors" – 15 years

"He can still have stubborn moments. He always likes to be punctual. He tends to talk loudly so [we] have to quieten him down often in public. He talks freely to people even if he has just me there! As well as talking, he loves computer games, TV, football and looking after pets. – 17 years

Sleep problems

Sleep problems were common and should be anticipated, and clear sleep regimes set in place in early babyhood. Ten Unique families suffered severely from their child's disrupted sleep patterns. The age at which children outgrew their sleep disruption was extremely variable.

Puberty and Fertility

In many people it seems that the onset and progress of puberty started at the expected time and proceeded normally. However, there have been reports, both at Unique and in the medical literature, of people who have delayed puberty – this seems to be especially common in males. There are also reports in the medical literature of failure to develop secondary sexual characteristics and premature menopause (Sperber 1975; Kosztolanyi 1976; Riccardi 1977; Theilgaard 1977; Kurtyka 1988; Unique).

As various body tissues can contain T8M cells or be free of them, it is possible that in some people with T8M the tissue from which the eggs or sperm are derived has a normal chromosome make-up. Certainly, women with T8M have had children of their own

unaffected by their chromosome condition. There are no reports of men with T8M having children but analysis of sperm shows that they may be fertile, although some sperm may carry the extra chromosome 8. Because of these uncertainties, it is important that anyone considering a pregnancy should have genetic counselling (Habecker-Green 1998; Robinson 2002; Rauen 2003; Unique).

Adults with T8M

Unique has produced a separate guide to Adults with T8M. It is available to download from Unqiue's website: www.rarechromo.org.

Identifying T8M in pregnancy

Identifying and diagnosing T8M in pregnancy is not entirely straightforward. Finding trisomy 8 cells together with cells with a normal chromosome make-up in a chorionic villus sample (CVS), which comes from the developing placenta, or in amniotic fluid, does not necessarily mean that the baby will have T8M.

Maternal serum alpha-fetoprotein has been reported to be elevated in association with T8M (Van Haelst 2001). Follow-up investigations, including amniocentesis and especially fetal blood sampling, are required for prenatal diagnosis of T8M. Unfortunately, both a normal amniocentesis and a normal fetal blood sampling result cannot completely rule out chances of fetal T8M, and the detection of any abnormality on prenatal ultrasound indicates that the baby might be affected.

Detecting T8M in CVS

If the CVS shows T8M it will be investigated further, because in most cases it represents a state known as confined placental mosaicism. In confined placental mosaicism, cells in the developing placenta contain the extra chromosome 8 but the cells in the baby do not. In a large study of chromosomal mosaicism detected on CVS, T8M was found in 11 women. However, only one baby had trisomy 8 cells, so the remaining ten had confined placental mosaicism (Hahnemann 1997). There are two ways of checking chromosomes after CVS, known as direct testing and long term culture. The most accurate results come from long term culture, but in either case detailed ultrasound scans will be offered to check the baby carefully.

Diagnosing T8M from amniotic fluid

Amniotic fluid contains some cells shed by the baby, and by examining these cells it may be possible to be more certain about whether the baby is affected by T8M or not. However, as amniotic fluid, like chorionic villus tissue, can also contain cells from tissues other than the baby, the results of even an amniocentesis are sometimes not clear (Hsu 1997; Chen 2011). In order to get as complete and accurate a picture as possible, the results are usually considered together with the results of detailed ultrasound scans. In some centres it is also possible to examine cells exclusively from the baby by taking a blood sample from the umbilical cord.

What do these results mean?

Having repeated tests that can sometimes give unclear results is an extremely stressful experience. You should have the chance of an unhurried discussion of the outcomes with a geneticist before reaching any decisions about what to do next.

How did this happen?

The reason for an individual having an extra chromosome in some cells of their body is not yet perfectly understood. What is known is that the presence of three copies of a chromosome may arise in two main ways. It can be due to a process called non-disjunction: instead of cells dividing and duplicating themselves evenly, keeping the same chromosome number in all of the duplicated cells, one pair of chromosomes does not divide evenly. This can lead to an extra chromosome (in this case, an extra chromosome 8) in the fertilised egg, leading to full trisomy 8. At an early stage of development, one chromosome 8 is lost in a process called trisomy rescue. Two different cell lines, one with the extra chromosome 8 and the other without, develop at the same time, leading to T8M. Non-disjunction can also happen during mitosis, the process of cell division after fertilisation. In this case, the fertilised egg starts with the correct number of 46 chromosomes but following the mistake in cell division, a cell line with trisomy 8 (so with 47 chromosomes in all) develops at the same time as a cell line with the correct number of 46 chromosomes. Cells with trisomy 8 continue to duplicate themselves in certain organs and tissues.

At the same time, cells with the normal number of chromosomes duplicate themselves in other organs and tissues. Depending on when the non-disjunction happened, the person may have few or many cells with trisomy 8.

Why did this happen?

There is a lot more to be learned about why non-disjunction occurs but current understanding is that it occurs by chance. No parent has control over the process or can influence the number of chromosomes their child receives.

Can it happen again?

T8M is held to be a chance event that typically carries a very low recurrence risk for the individual's parents and family. Unlike other conditions involving non-disjunction, like Down syndrome, T8M is not linked with a mother's or father's age at conception.

A 5-year-old boy with T8M and his baby sister who has normal chromosomes

Notes

Inform Network Support

Understanding chromosome disorders Unique

Rare Chromosome Disorder Support Group,
G1, The Stables, Station Rd West, Oxted, Surrey. RH8 9EE
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

There are two Facebook groups for families affected by T8M:

- Trisomy 8 Mosaicism
- I know a person with Mosaic Trisomy 8 and I think that they're great!!

www.facebook.com

Websites, Facebook groups and other links:

Project 8p: Join
Project 8p: Patient Navigator

Join Unique for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can please make a donation via our website at
www.rarechromo.org
Please help us to help you!

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

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 Anne Slavotinek, Professor of Clinical Pediatrics, Universtiy of California, USA and by Professor Maj Hultén, Professor of Medical Genetics, University of Warwick, UK

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