Understanding Chromosome & Gene Disorders

10q25 and 10q26 deletions

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10q deletions: breakpoints in 10q25 or 10q26

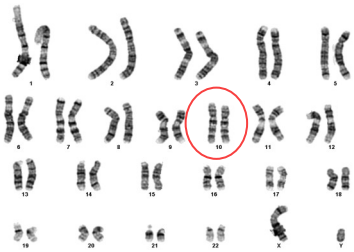
A 10q25 or 10q26 deletion means that the cells of the body have a small amount of genetic material missing from one of their 46 chromosomes – chromosome 10. For healthy development, chromosomes should contain just the right amount of genetic material (DNA) – not too much and not too little. Like most other chromosome disorders, having parts of chromosome 10 missing may increase the risk of health conditions that are present from birth (congenital disorders), developmental delay and intellectual disability/learning difficulties. It is important to remember that the outcome of having a 10q deletion is variable and depends on a number of factors, including what and how much genetic material is deleted.

Background on Chromosomes

Chromosomes are structures found in the nucleus of most of the body's cells. Every chromosome contains hundreds to thousands of genes, which may be thought of as individual instruction booklets that contain all the genetic information telling the body how to develop, grow and function.

Chromosomes (and genes) usually come in pairs with one half of each chromosome pair inherited from each parent. Humans have 23 pairs of chromosomes (to give a total of 46 individual chromosomes).

Apart from the sex chromosomes (usually two Xs for a girl and an X and a Y for a boy), chromosomes are numbered 1 to 22, approximately from largest to smallest.



Chromosome pairs 1-22, X and Y (male). Chromosome 10 pair circled in red

Chromosome Deletions

A sperm cell from the father and an egg cell from the mother each carries just one copy of each chromosome. When they join together at fertilisation, they form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the genetic material) in order to produce the billions of cells that are necessary for human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and

Sources

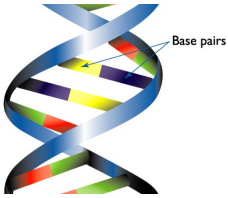
The information in this leaflet is drawn partly from published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from Unique. In addition, this leaflet draws on information from two surveys of members of Unique conducted in 2004 and 2008/9, and information available in Unique's database, referenced Unique. Note: an update of this guide was carried out in 2021/2 based on published medical literature and Unique's database (it was not possible at that time to carry out a survey of Unique members).

replication process, parts of the chromosomes can break off or become arranged differently from usual.

People with a 10q25 or 10q26 deletion have one unaffected chromosome 10, but a piece from the long arm of the other chromosome 10 is missing or deleted. The first published description of a person with a 10q25 or 10q26 deletion was in 1978. There have since been well over 100 reported in medical literature worldwide. The deletion is believed to occur in equal frequency in males and females (Lewandowski 1978; Faria 2016; Sutani 2020).

Looking at 10q

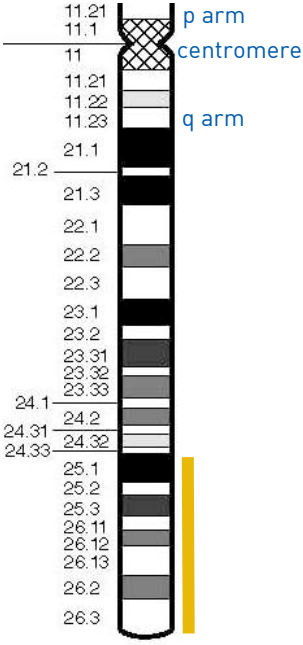
Chromosomes can't be seen with the naked eye but if they are stained and magnified under a microscope it is possible to see that each one has a distinctive pattern of light and dark bands that look like horizontal stripes.



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

Each chromosome contains millions of base pairs of DNA. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure. There are millions of base pairs in every chromosome, and they are often counted in millions, where 1 Mb equals one million base pairs.

Bands 10q25 and 10q26 contain around 29.7 million base pairs. This sounds like a lot, but it is actually less than 1 per cent of the DNA in each cell.



Each chromosome has a short (p) arm and a long (q) arm. The bands are numbered outwards starting from the point where the short and long arms meet (the centromere). A low number such as q11 is close to the centromere; this part of the arm that is fairly close to the centromere is called the proximal part. A higher number such as q25 is closer to the end of the chromosome, in the part referred to as distal. The term cen is used to indicate a location that is very close to the centromere, while ter (for terminal) indicates a location that is very close to the end of the p or q arm.

Distal 10q deletions

Some 10q25 and 26 deletions are interstitial, where a piece of the long arm of chromosome 10 is missing but the tip (and possibly more than just the tip) is still present. The majority of deletions involve 10q26 and are terminal, meaning that the tip of the long arm of chromosome 10 is included in the deletion. Such deletions are associated with a well-recognised

condition called 10q26 deletion syndrome (MIM #609625) (also know as 10qter deletion, chromosome 10q26 deletion syndrome, distal 10q deletion syndrome, distal deletion 10q, distal monosomy 10q, monosomy 10qter, telomeric deletion 10 or terminal chromosome 10q26 deletion syndrome). The features associated with 10q26 deletion syndrome vary widely from person to person, even among members of the same family, but the most common features are detailed on page 6 (Petersen 1998; Scigliano 2004; Choucair 2015; Tanteles 2015; Vera-Carbonell 2015; Faria 2016; Ramos 2016; Lacaria 2017; Li 2020; Unique).

Note: Hereafter in this leaflet, deletions involving 10q25 and/or 10q26 will be referred to as 10q25/6 deletions.

In 2009, Unique had 69 members with a pure 10q25/6 deletion without loss or gain of material from any other chromosome. By 2021, this number had reached over 200.

Many more people, described in medical literature and members of Unique, had a loss or gain of material from another chromosome arm as well as a 10q25/6 deletion, usually as a result of a chromosome change known as a translocation. It is only those individuals with a "pure" 10q25/6 deletion and no other known chromosomal anomaly whose data was used to compile this guide since, for others, the reason for any observed features may be due to the other chromosomal change(s). This guide may nonetheless be of help to explain some of their features.

Genetic tests

With any deletion the amount of deleted DNA can vary. Deletions that are so small that they are not visible under the microscope using standard techniques, as may be the case for deletions involving 10q25/26, are called microdeletions. Many people who have a microdeletion may therefore have previously been told their standard chromosome analysis was 'normal'.

A laboratory technique called FISH (fluorescence *in situ* hybridisation) enables sections of the chromosome to be analysed in more detail and can help detect a deletion. This technique uses fluorescently-labelled pieces of DNA that match the DNA in specific places on a chromosome so this test would have been offered only if there was a suspected anomaly in a specific region of a chromosome.

The more commonly used test nowadays is called chromosomal microarray (CMA) and allows genomic DNA to be analysed in greater detail. An array test can detect very small deletions even when this diagnosis is not suspected. It will also identify a more precise position on the chromosome for the piece of DNA that has been deleted.

Advances in next generation sequencing (NGS) technologies offer the promise of ever -more accurate diagnoses and understanding of rare chromosome disorders. NGS allows multiple genes; the entire protein-coding portion of all the genes in the genome (whole-exome sequencing (WES)); or even the entire genome (whole-genome sequencing (WGS)), rather than just targeted regions or individual genes, to be sequenced. This allows variation across the entire genome to be assessed and may be particularly useful for detecting microdeletions (and microduplications) that may be missed by less sensitive microarray analysis (See Unique's guide to DNA Sequencing for more details).

Chromosome test results

The results of genetic (genomic) testing are likely to be given to you by your geneticist or a genetic counsellor. They will talk you through the results and can also tell you more about the genes and chromosome material that have been deleted.

Depending on the test that was carried out, someone with a deletion including 10q25/26 might have results that look like one of these examples:

46,XX,del(10)(q25.3)dn

46	The total number of chromosomes in your child's cells
XX	The two sex chromosomes, XY for males; XX for females
del	A deletion, or material is missing
(10)	The deletion is from chromosome 10
(q25.3)	The chromosome has one breakpoint in band 10q25.3, and material from this position to the end of the chromosome is missing
dn	The deletion occurred *de novo* (or as a "new event"). The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 10q25.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child

arr[hg19]10q26.2q26.3(129,634,839_135,506,703)x1pat

arr	The analysis was by array-CGH
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about

Genome Assemblies

The human genome project, an international effort to sequence the entire human genome and map all of its genes, was announced complete in 2003.

However, there were many gaps in the sequence and mapping data, and scientists have since been working continuously to identify the missing information. When new sequence information is identified, the base pair numbers of each chromosome change slightly and hence the numbers for individual genes and duplications can shift.

Each new version of the genome is often referred to as an 'assembly'. Every few years a new assembly is released. The genetic information you are given will be based on the Genome Reference Consortium (GRC) human (h) genome assembly that was the most up-to-date at the time the test was carried out. Therefore, you may see the DNA sequence referred to as hg19 (human genome 19) (on your child's genetic report it may also be referred to as GRCh37), which was released in 2009, or hg 18, which was released in 2006. The lower the hg number, the earlier the release.

At the time of writing, the databases commonly used by clinical geneticists and *Unique* were moving to a more recent assembly named GRCh38/hg38, which was released in 2013. Genetic reports are also now starting to use coordinates based on the GRCh38 assembly and it is important to remember that genes and genetic changes may have new locations and base pair numbers depending on the assembly used.

	the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted (*see* blue box)
10q26.2q26.3	Chromosome 10 has two breakpoints, one in band 10q26.2 and one in band 10q26.3
129,634,839-135,506,703	The base pairs between 129,634,839 and 135,506,703 have been shown to be deleted. Take the first long number from the second and you get 5,871,864 (5.88Mb or 588kb). This is the number of base pairs that are deleted.
x1	means there is one copy of these base pairs (the expected copy number is two – one on each chromosome 10), so this is a deletion
pat	The anomaly has been inherited from the father (pat)

Most common features

Every person with a 10q25/6 deletion is unique and so each person will have different medical and developmental concerns; there is known to be considerable variability, even within families with the same deletion. Additionally, no one person will have all of the features listed in this leaflet. However, a number of common features have emerged and include:

- Growth delay both in the womb and after birth
- Feeding difficulties
- Hypotonia (floppiness or unusually low muscle tone) in new-born babies
- Variable disabilities in learning, speech and motor development. Children will often need support with learning although the amount of support needed by each child will vary
- Problems with vision/structural eye anomalies, including strabismus (squint)
- Kidney and/or urinary tract anomalies
- Heart conditions, though the majority of reported cases are minor and often resolve naturally without surgical intervention
- Microcephaly (an unusually small head)
- Genital anomalies, most commonly cryptorchidism (undescended testes) in boys
- Characteristic facial features
- Seizures
- Attention deficit/hyperactivity disorder, impulsivity or autism/autistic traits

Does the breakpoint matter?

The size of the deleted region found in those with 10q deletions varies widely, ranging from small microdeletions to much larger deletions. What we know from medical literature and Unique members suggests that the majority involve a deletion with a break in q26 (in 2021, Unique had 32 members with a break in q25 and 202 members with a break in q26, and no other known loss or gain of genetic material (see next page)).

The clinical features observed in people who have smaller terminal deletions are mainly the same as those in people with larger deletions (Lopes 2017), suggesting that it is deletion of the most distal part of chromosome 10q that leads to most of these features (*see* Hypotonia, Ataxia and Delayed Development Syndrome (HADDS)). While there are cases of individuals with a larger deletion who are affected relatively mildly without any major birth anomalies, it is notable that two individuals who appear to be among the most mildly affected and only discovered the deletion after they passed it on to their children, had small deletions with breakpoints in 10q26.2, meaning the deletion did not include10p26.3 (the most distal part of chromosome 10q) (Irving 2003; Choucair 2015; Ramos 2016; Unique).

Breakpoints in Unique families

Bracketed numbers show numbers of members in the Unique database (2021).
These breakpoints are recorded for members of Unique with a 'pure' terminal 10q25/26 deletion:

10q25.1 - qter (7)
10q25.2 - qter (3)
10q25.3 - qter (6)
10q26 – qter (33)
10q26.1 – qter (27)
10q26.11 – qter (2)
10q26.12 – qter (2)
10q26.13 – qter (4)
10q26.2 – qter (9)
10q26.3 – qter (33)
Unspecified 10q terminal deletion - (1)

These are the breakpoints recorded for members of Unique with interstitial deletions:
10q25q25 (1)
10q25.1q25.1 (1)
10q25.1q25.2 (1)
10q25.1q25.3 (2)
10q25.1q26.11 (1)
10q25.2q25.3 (3)
10q25.2q26.1 (3)
10q25.2q26.11 (1)
10q25.2q26.13 (2)
10q25.3q26.11 (1)
10q26.1q26.1 (3)
10q26.11q26.12 (1)
10q26.11q26.13 (3)
10q26.11q26.3 (3)
10q26.11q26.3 & 10q26.2q26.3 (1)
10q26.12q26.13 (2)
10q26.12q26.2 (1)
10q26.12q26.3 (5)

10q26.13q26.13 (1)
10q26.13q26.2 (3)
10q26.13q26.3 (26)
10q26.1q26.3 (2)
10q26.2q26.2 (2)
10q26.2q26.3 (28)
10q26.3q26.3 (10)

Hypotonia, Ataxia and Delayed Development Syndrome (HADDS)

In 2016, a novel neurodevelopmental syndrome named hypotonia, ataxia and delayed developmental syndrome (HADDS) (MIM #617330), was co-discovered by three independent research teams (Chao, Davids et al 2016, Harms et al 2016, Sleven et al 2016). HADDS is usually caused by variants (changes) in the nucleotide sequence of one copy of a gene called Early B-Cell Factor 3 (*EBF3*), which is located near the tip of chromosome 10 in 10q26.3. However, deletion of only the *EBF3* gene can also cause HADDS (Lopes 2017). It is thought that when one copy of the *EBF3* gene doesn't function properly or is missing, the remaining copy of the *EBF3* gene on the unaffected chromosome 10 cannot produce enough of the gene product to allow its normal function, a situation known as haploinsufficiency. In this case, the gene product is a type of protein called a transcription factor (TF). TFs play a role in regulating other genes, in the case of EBF3 turning on and off genes involved in the development of the nervous system, as well as other body systems.

HADDS is most commonly associated with some degree of developmental delay and intellectual (learning) disability; speech delay; ataxia, which can result in issues with balance and a lack of muscle control or co-ordination; hypotonia (low muscle tone); autism or autism-like traits; attention deficit disorder (ADHD); eye and vision concerns; failure to thrive or delayed growth; urology issues that may affect the kidneys, bladder or genitals; a high pain threshold; and characteristic facial features. Additional possible features include seizures, insomnia, neurogenic bowel dysfunction, constipation and issues with feeding/swallowing. Head circumference is typically age appropriate. Neuroradiologic findings include variable alterations in the structure of the parts of the brain called the cerebellum and the corpus callosum (Deisseroth 2022). It is important to note that there is considerable variability in the degree to which individuals are affected by HADDS and for each individual with HADDS, not all these features will be present. It has also been suggested that motor skills are less affected by deletion of the *EBF3* gene than by variants in the gene.

The strong overlap in the features of 10q26 deletion syndrome and HADDS suggests that it is deletion of one copy of the *EBF3* gene that may be the principal cause of the features associated with distal 10q deletions, although other genes are believed to play a role in some features (*see* Ongoing research into 10q25/6 deletions) (Sleven et al., 2017; Chao et al., 2017; Harms et al., 2017; Blackburn et al., 2017; Lopes 2017; Tanaka 2017; Deisseroth 2020; Li 2020; Sutani 2020; Huang 2021; Nishi 2021; Padhi 2021; The EBF3-HADDS Foundation - provides support and information for families affected by HADDS (www.hadds.org/).

Are there people with a 10q25/6 deletion who are healthy and have no major developmental or medical concerns?

In a few people (usually with deletions in the 10q26.2 band), the deletion appears to have a milder effect. A 40-year-old woman with mildly asymmetrical ears only discovered that she carried a 10q26.2 deletion after her 9-year-old daughter was found to have a 10q26.2 deletion. A 63-year-old woman and two of her daughters (37 and 38 years), all of whom had a 10q26.2 deletion, all attended mainstream school and were in full-time employment. A woman with a 10q26.3 microdeletion had no developmental delay and had reached developmental milestones ahead of time (Irving 2003; Unique).

What is the outlook?

There are some older reports in the literature of neonatal death, most commonly due to severe cardiac problems. Progress in the management of cardiac disease has improved the prognosis of babies with cardiac anomalies. For children with no serious heart or other organ problems, lifespan should not be significantly affected (Mulcahy 1982; Taysi 1982; Wulfsberg 1989; Unique).

While the outlook depends on a child's individual progress it is likely that most children with a 10q25/6 deletion will continue to need support throughout their lives.

Pregnancy and birth

Many mothers carrying babies with 10q25/6 deletions experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, pregnancy complications are not uncommon in mothers carrying a baby with a 10q25/6 deletion.

Babies are often small for gestational age or are described as having intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb has slowed resulting in babies that are smaller than expected for the number of weeks of pregnancy. Babies may also show little fetal movement while in the womb. A number of parents told us about unusual findings when undergoing ultrasound scans. A two-vessel umbilical cord was observed in two babies; a kidney anomaly was detected in one baby; increased fluid around the baby was seen in several pregnancies; ureteral reflux was detected in one baby; and one baby was diagnosed with hydronephrosis. There were also several cases in the published medical literature in which urinary tract anomalies were detected on prenatal scans (Scigliano 2004; Unique).

One Unique family discovered a 10q25.2q26.13 deletion before their baby was born, when an amniocentesis was performed after a nuchal scan showed an increase in fluid at the back of the neck. There are several examples in medical literature of prenatal diagnosis of a 10q25/6 deletion: in one case for advanced maternal age and in another after IUGR and heart anomalies were detected during an ultrasound scan. The parents, in both these cases, chose not to continue with the pregnancy (Chung 1998; Kerher-Sawatzki 2005; Unique).

Premature birth appears to be slightly more likely than for other babies. In one research study 39 per cent of babies (7/18) were born between 32 and 37 weeks. Among Unique members in 2009, 12 per cent (6/47) were born before 37 weeks (Wulfsberg 1989; Unique).

Newborn

Many babies with 10q25/6 deletions need help to establish breathing or experience spells of apnoea (pauses in breathing) and some may need extra oxygen within the newborn period. Reflexes (such as the startle reflex) may not be as expected and in particular your baby may show a very weak sucking ability. Babies are sometimes exceptionally sleepy. Typically, babies with a 10q25/6 deletion have a very faint cry or do not cry audibly (Wulfsberg 1989; Leonard 1999; Shapiro 1995; Piccione 2008; EBF3 -HADDS Foundation; Unique).

Growth and feeding

Babies are often, but not always, small and underweight at birth. In 2009, regardless of the breakpoint, birth weights recorded at Unique showed a considerable variation with an average of 2.94 kilos (6lb 8oz). Around a third of these Unique babies had a low birth weight (below 2.6 kilos or 5 lb 12oz) at term (Unique).

Range of birthweights at Unique in 2009 (at or near term):

1.814 kilos (3lb 16oz) to 4.11 kilos (9lb 1oz)

A short stature is common. One study reports that 40 per cent of babies have growth delay at birth but 75 per cent are described as being growth delayed later in babyhood or childhood (Wulfsberg 1989; Faria 2016; Lacaria 2017; Lopes 2017; EBF3-HADDS Foundation; Unique).

Feeding difficulties are a major area of concern for families, particularly as babies usually start out small and underweight. The hypotonia that is common in babies with a 10q25/6 deletion can lead to difficulties with sucking and swallowing, and/or latching onto the breast. Babies with a cleft or high palate can also find the action of sucking and swallowing difficult. Many babies have a small appetite and struggle to finish a feed. Fifteen of the 29 mothers surveyed by Unique in 2009 attempted to breastfeed their babies, although only four established breastfeeding. However, a number of babies were bottle-fed expressed milk. Seven out of 39 Unique babies benefited from a temporary nasogastric tube (NG-tube, passed up the nose and down the throat). As some of these babies matured enough to suck effectively, the NG-tube could be removed and breast- or bottle-feeding established. A further four babies who initially benefited from temporary NG-tubes later needed gastrostomy tubes (a G-tube, feeding direct into the stomach) in order to meet their nutritional needs (Unique).

4 years old with a 10q25.2q2613 deletion

Hypotonia (low muscle tone) can also affect their food passage and contribute to gastro-oesophageal (GO) reflux (in which feeds return readily up the food passage). In the 2009 Unique survey, almost a third of babies had reflux. This can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. If these measures are not enough, some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (EBF3-HADDS Foundation; Unique).

Some older babies and toddlers have trouble chewing and can choke or gag on lumps in food so may continue to eat puréed food for longer than their peers and the start of eating finger foods may be delayed. Parents have found that modifying the texture of foods by grating, mincing, chopping or adding sauces to foods can help to overcome these problems. Children often continue to be slow, fussy eaters although some children develop large appetites and a love of food. As a result of these feeding difficulties a number of families have consulted a dietician (EBF3-HADDS Foundation; Unique).

However, a 3-year-old had no feeding problems and a 2-year-old was described as 'always a good eater'. Another who had problems sucking as a baby had no feeding problems at age 2 years. A 17-year-old had a good appetite and loved vegetables! (Unique)

> ❝ She is still a poor eater and only likes certain foods, especially milk, pudding and porridge. ❞ – *7 years*

> ❝ She was fed with a NG-tube for the first year and a half but kept pulling it out so it was decided she needed a G-tube, which she used for six years until she started going to special school where she learned to eat by mouth, both by imitation of the other kids and because she received speech therapies that helped her to eat by mouth. The G-tube was removed last year. ❞ – *8½ years*

> ❝ He had a weak suck. We tried breastfeeding for quite some time and were not successful. He was bottle fed expressed breast milk for 4 months. ❞ – now *9 years*

6 years old with a 10q25.2q26.1 deletion
Feeding with a G-tube

Appearance

Children with 10q25/6 deletions sometimes have facial features in common. Typically, babies have a small head (microcephaly) with a broad nasal bridge with a beaked or prominent nose. They may have a triangular and sometimes asymmetrical face with unusually-formed, low-set ears. They may have deep-set eyes or widely-spaced eyes (hypertelorism) or there may be an extra fold of skin covering the inner corner of the eye (epicanthic folds). They often have a thin bow-shaped upper lip with a small, receding lower jaw (micrognathia). A short neck which is sometimes webbed is also common. However, many children look little different compared to other children and may closely resemble their siblings or parents (Faria 2016; Lin 2016;Ramos 2016; Lacaria 2017; Lopes 2017; Li 2021; Deisseroth 2022; EBF3-HADDS Foundation; Unique).

Learning

Learning difficulties and intellectual disability are common in children with a 10q25/6 deletion, with most children moderately affected and a small minority severely affected. As always, there is individual variation, and a few children have mild, borderline or even no learning difficulties. However, most children will need support and benefit from early intervention programmes and may thrive best in a special learning environment. Around half of Unique children attend mainstream school, often receiving some learning support or 1:1 help in the classroom, with the other half benefiting from a special education school (Faria 2016; Lin 2016; Ramos 2016; Lacaria 2017; Lopes 2017; EBF3-HADDS Foundation; Unique).

Many children learn to read and write. The Unique experience is those who master reading start to recognise words between the ages of 4 and 8 years (with an average of 5½ years). Those mastering writing start forming letters between the ages of 4 and 10 years (with an average of 5½ years). For some children, hypotonia can make writing or drawing difficult and many children find using a keyboard to write easier than a pencil or pen. This level of achievement is not possible for all children and a number do not master reading or writing, although some can recognise their own name and make simple drawings. Children generally have a good memory. A number of children are hyperactive or are described as being easily distractible or having a short attention span, which can make learning more of a challenge (*see* Personality & Behaviours). Children with 10q25/6 deletions seem to share a love of music and singing (Unique).

> “ He has a good memory and it is only necessary to show him how to use a toy once and he knows how to turn it on/off. He loves music and has a lovely, bubbly, cheeky personality. ” – *2 years*

> “ He knows all the colours and body parts very well. He can stack blocks, use shape sorters and do simple puzzles. ” – *2½ years*

> “ She has a great memory, can read three letter words and some others. She has problems drawing pictures and writing. She writes most letters but at angles, disconnected and sloppy. ” – *5 years*

> “ She reads well and has an excellent memory although she has poor focus. She needs a quiet area where not much is happening in order to learn, otherwise she becomes overwhelmed and too excited. ” – *4 years*

❝ She learned to read at 5-6 years and reads short sentence books with help. She does not choose to read alone. She has an excellent memory. ❞ – *7½ years*

❝ He achieves at or above his grade level in all academic subjects and has an excellent memory. He has an excellent ear for music and plays the piano. He reads everything! He had a touch screen computer from the age of 2 years and became comfortable with it so that he can use the keyboard and computer to complete assignments even though his handwriting is not legible ❞ – *9 years*

❝ She has a very good memory and is very good at maths. She reads any book she is given! She is in mainstream school with 1:1 support. ❞ – *9½ years*

❝ She loves music and has a great rhythm. She has an excellent memory and learned to read at 6 years. It took some time to understand maths. ❞ – *10 years*

❝ She has a fantastic memory. She can read some simple words (cat, milk, mum, dad, go, to, and, the, up). ❞ – *11 years*

❝ She reads children's picture books with few sentences. Her writing is large and all over the place. ❞ – *18 years*

❝ She reads effectively and buys magazines. She has good, clear handwriting and basic computer literacy. ❞ – *23 years*

Speech and communication

Many children with a 10q25/26 deletion learn to speak well. However, babies tend to cry very little and some do not cry audibly until 18 to 24 months. Speech, too, is almost always delayed, with first words usually emerging between the ages of two and six years. Some children continue to have articulation difficulties (apraxia of speech), with consonant sounds often proving more difficult, and/or their speech may sound 'slurred'. Many children use sign language, PECs (picture exchange communication system) and/or computer-based approaches to help to communicate their needs and wants. Often, as speech is mastered, they find they no longer have need of these aids. Evidence in the literature, which is also backed up at Unique, suggests that many children have better receptive language than expressive language: they understand more than they can express. Many children continue to have articulation difficulties, with consonant sounds often proving more difficult, and/or they may stutter or have 'slurred' speech. Speech therapy has proved extremely beneficial to many children and children can go on to speak in complex sentences and have a very large vocabulary, although the articulation difficulties may remain. There is a very small minority of children known to Unique who do not master language and continue to use gestures, facial expressions and vocal noises to indicate their needs and express their feelings (Teyssier 1992; Lukusa 2000; Piccione 2008; Ramos 2016; EBF3-HADDS Foundation; Unique).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which, in addition to insufficient sucking, can also affect the development of speech. Those with a cleft or high palate may also have specific difficulty with certain sounds. Any concerns around hearing should also be acted on early to help reduce any impact on speech (EBF3-HADDS Foundation; Unique).

❝ He currently knows about 150 signs and his vocalisation is improving a lot. ❞ – *2½ years*

❝ A recent evaluation showed her to be above average in comprehension and use of language; however, it is selective. ❞ – *4 years*

❝ She has always been very keen to communicate and uses a combination of signing and speech and gestures. She is now using more speech than noises but has to be reminded often to use words. ❞ – *4 years*

❝ She doesn't use words but she points, cries and looks at pictures to communicate. ❞ – *4 years*

❝ He has fluent speech now but this was acquired late and needed therapy. He initially experienced some processing delay but now speaks in long sentences using polysyllabic words. ❞ – *4 years*

❝ She said a few words at 2 years but did not progress further until 6½ years and has improved since. She now speaks in sentences and is generally understood by everyone. ❞

❝ She used to use signing but stopped as she began talking. ❞ – *7½ years*

❝ He uses very developed speech but still has significant articulation difficulties. ❞ – *9 years*

❝ He talks very fluently now although used sign language initially. He still finds certain sounds difficult but he can be understood and 'talks the hind legs off a donkey'! ❞ – *9 years*

❝ She communicates well. She still has speech problems but speaks in 5/6 word phrases although sometimes not in the correct order. ❞ – *9½ years*

❝ She talks but pronounces words differently; she says 'ralad' instead of salad and 'tamel' instead of towel. ❞ – *11 years*

❝ She speaks in sentences and uses signs, but she is hard for new people to understand. ❞ – *18 years*

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

Children with a 10q25/6 deletion are typically slow to reach their developmental motor milestones.

The Unique experience in 2009 was that babies started to roll between 3 months and 15 months (average 7 months); sit between 6 months and 4½ years (average 19 months) and crawl between 9 months and 2½ years (average 16 months). Some children, however, did not crawl but instead moved around by bottom shuffling. In this group, independent walking was mastered between 14 months and 6 years (average 2½ years).

Some children need support (such as a standing frame, walking frame, support boots, a supportive Lycra 'second skin' and/or leg braces) while learning to walk. Most children go on to walk, climb stairs and run, although they can be unsteady with poor balance (ataxia) and co-ordination, which may put them at increased risk of falls. Many children walk with a wide gait and trip easily (Petersen 1998; Scigliano

22 months with a 10q26.13q26.3 deletion

2004; Ramos 2016; Lin 2016; Lacaria 2017; Lopes 2017; Li 2021; EBF3-HADDS Foundation; Unique).

There are several reasons for these motor delays, including hypotonia. A few children have increased muscle tone (hypertonia), which in some cases may develop as children approach puberty, or varying muscle tone (hypotonia in some parts of the body and hypertonia in others). Hypotonia often improves as children mature; nonetheless, early physiotherapy and occupational therapy can be beneficial. Some children find it hard to fully straighten their elbows or knees and this can make walking and physical activities difficult. Physical activities enjoyed by some children at Unique include swimming, riding a tricycle, bicycle or scooter, playing football, trampolining, ballet, skiing and dancing (Mehta 1987; Wulfsberg 1989; Leonard 1999; Tanabe 1999; Waggoner 1999; EBF3-HADDS Foundation; Unique).

❝ He lacks some of the physical skills of his peers but can swim and has generally advanced rapidly with support and therapy. ❞ – *4 years*

❝ She is very active. When she was young she took a while to walk and never crawled but you can't stop her now! ❞ – *9½ years*

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

Hypotonia and hypertonia can also affect fine motor skills in children with a 10q25/6 deletion 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. A small number of children have been reported with hyperreflexia: overactive reflexes which can result in twitching and can also affect fine motor skills. Many children have occupational therapy in order to help improve these skills (Gorinati 1989; Petersen 1998; Leonard 1999; Waggoner 1999; EBF3-HADDS Foundation; Unique).

As a result of these difficulties, children are likely to continue to need help with dressing and undressing. They will also require assistance in tasks such as brushing teeth and washing. Toilet training is also likely to be affected. The information at Unique suggested that consistent toilet training was often mastered between 2 years and 8½ years (average just over 4 years); however, this level of training has not been possible for all children with some children achieving bowel and bladder control during the day but not at night. One child was toilet trained during the day at 8 years old but regressed at 17 years and is now doubly incontinent; another was fully toilet trained at 5 years old but regressed when her baby sister arrived (Unique).

❝ She was completely toilet trained by 3½ years. She dressed herself by the age of 3 years. She now needs help with brushing her teeth and washing her hair but can wash her own hands. ❞ – *4 years*

❝ He has very poor fine motor skills and is a very messy eater and writer. ❞ – *9 years*

Medical concerns

Kidneys and urinary tract

Unusual features of the kidneys and urinary tract appear to be common in children with 10q25/6 deletions (and are a common feature of HADDS) and your baby may have a renal scan. Almost a third (10/36) of those surveyed by Unique in 2009 had a kidney anomaly, a figure which is backed up by medical literature. Among the problems reported at Unique and/or in published medical literature are anomalies where the ureters (the tubes that carry urine from the kidneys) enter the bladder; an obstruction in the valves that let urine flow out from the bladder; underdeveloped (small) kidneys or enlarged kidneys (hydronephrosis); a duplex kidney; and kidney (vesico-ureteral) reflux (where the urine flows upwards from the bladder back up to the kidney, potentially damaging the kidneys). For those affected by kidney reflux, ureteral re-implantation may be necessary. This surgical procedure is performed when the ureters do not join the bladder in the correct place which can cause kidney reflux. The procedure disconnects the ureters from the bladder and reconnects them in the correct place. Urinary tract infections are also common, affecting around a quarter of those surveyed by Unique (Scigliano 2004; Courtens 2006; Motoyama 2008; Lin 2016; Ramos 2016; Lacaria 2017; EBF3-HADDS Foundation; Unique).

Heart conditions

Heart (cardiac) conditions have been reported to affect up to half of all babies born with a 10q25/26 deletion. The most common conditions reported include persistence of prenatal cardiac structures such as persistent ductus arteriosus (PDA; where the channel between the aorta and the pulmonary artery that takes blood to the lungs fails to close after birth), which often resolves without the need for surgical intervention, although surgery may be necessary in some cases. Holes between the upper or lower chambers of the heart (ventricular septal defects (VSD) or atrial septal defects (ASD)) have also been reported. Again, in many children these defects heal (close) naturally without surgery. Several babies had a heart murmur, which was often "innocent" (meaning there is no structural heart problem and no treatment is required). Other conditions that have been observed include mitral valve prolapse (one or both flaps of the valve are enlarged) and bicuspid aortic valve (the valve that regulates blood flow from the left ventricle into the aorta has two flaps instead of the usual three). More rarely, complex heart conditions have been found, including Tetralogy of Fallot (involving four heart defects including both a VSD and pulmonary stenosis) that requires surgical correction, and a hypoplastic left heart (Wulfsberg 1989; Petit 1998; Ogata 2000; Faria 2016; Lin 2016; Ramos 2016; Unique).

Heart conditions occur irrespective of breakpoints affecting those with breakpoints in 10q25 and 10q26 although there is some evidence that severe cardiac defects are less common in those with a subtelomeric (just above the telomere at the end of the chromosome) deletion (in 10q26.2 or 10q26.3) (Courtens 2006).

Circulation

Around 25 per cent of Unique families who took part in the survey reported that their child had a low body temperature or had difficulty maintaining the temperature in their hands and feet (a feature of HADDS). Families have told us that their child's hands and feet are often very cold and can turn a blue/purple colour at times, with the problem frequently worse after periods of inactivity, such as upon waking in the morning. One child who suffered cold hands and feet before she was fully mobile was no longer affected after she started to walk and become more active. Another Unique child's circulation seemed to be improving as she grew older (EBF3-HADDS Foundation; Unique).

Seizures

Seizures are caused by a change in electrical activity in the brain. Depending on the part(s) of the brain affected, symptoms vary but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Seizures are not a consistent feature of 10q25/6 deletions but any evidence of seizures should be acted on promptly. Electroencephalograph (EEG) and video telemetry (video EEG) are medical tests that can be used to measure and record the electrical activity of the brain, and are tools that, when used alongside other tests, can help diagnose the type of seizure experienced. Where necessary, treatment options, including the use of anti -convulsants such as valproate acid, sult(h)iame and Keppra, can help reduce the frequency and severity of seizures.

One in five of those who took part in the 2009 Unique survey suffered from at least one seizure, however many children only had one or few seizures and outgrew them. A number of other children's seizures were well controlled by medication, although two children out of 36 had seizures that had not been completely controlled by medication.

The published medical literature also describes children who suffer from seizures and one early study suggested that seizures are more common in those with a subtelomeric deletion. The study reported that 31 per cent of those with a subtelomeric deletion had seizures whereas seizures were only sporadically described in those with a larger deletion. The evidence at Unique does not back this up: seizures appear to affect those with small or large deletions with equal frequency. Various types of seizure are a feature of HADDS and may therefore be more likely to affect those with a deletion involving the *EBF3* gene (Wulfsberg 1989; Waggoner 1999; Lukusa and Fryns 2000; Lukusa 2002; Irving 2003; Courtens 2006; Piccione 2008; Lin 2016; EBF3-HADDS Foundation; Unique).

Vision

Strabismus (a squint), where one or both eyes can turn inwards, outwards or upwards, is the most common vision problem noted, with over 80 per cent of Unique children affected regardless of breakpoint. Many squints are convergent (the eyes cross) and many children need surgery to re-align the eyes. Strabismus is a common feature of HADDS and evidence in published medical literature has suggested that squints are more common in those with a subtelomeric deletion with breakpoints in 10q26.2 or 10q26.3 (Waggoner 1999; Scigliano 2004; Faria 2016; Ramos 2016; Lin 2016; Lacaria 2017; Lopes 2017; EBF3-HADDS Foundation; Unique).

15 years old with a 10q26.13q26.3 deletion

Other reported concerns, which are also common features of HADDS, include long– and short- sightedness and astigmatism (the cornea, the clear cover over the iris and pupil, is abnormally curved resulting in blurred vision). These problems are often mild and can be corrected with glasses.
A number of other anomalies have been reported in a few or individual cases. These include blocked tear ducts, which affected at least four Unique children; several cases of coloboma (when one or more structures in the eye don't fully develop during pregnancy); oculomotor apraxia (when there is difficulty controlling the movement of the eyes in a desired direction); nystagmus (rapid, uncontrolled eye movements); hypoplastic (underdeveloped) optic discs; cortical visual impairment (the visual systems of the brain do not consistently understand or interpret what the eyes see); and monocular vision (where each eye is used separately as opposed to the usual binocular vision where the eyes work together) (Waggoner 1999; Courtens 2006; Lukusa 2002; Courtens 2006; Ramos 2016; Lacaria 2017; Sutani 2020; Li 2021; EBF3-HADDS Foundation; Unique).

Hearing

More than half of Unique children surveyed in 2009 reported excessively sensitive or acute hearing and an exaggerated response to loud noises. Some children appear to outgrow this problem although for others it remained a concern (Unique).

Hearing impairment is common in children with chromosome disorders and affected almost a third of Unique children with this deletion. Several Unique children were diagnosed with sensorineural hearing loss (where there is a problem with either the auditory nerve, which transfers nerve signals to the brain, or damage to the tiny hair in the inner ear), but the most common cause of hearing impairment among these children appears to have been conductive hearing loss (where sound is not able to reach the inner ear), in these cases due to glue ear, where there is 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. This means 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) inserted into the eardrum. Occasionally, hearing aids or assisted listening devices may help as a temporary or longer-lasting measure. Hearing loss has also been reported in published medical literature, albeit infrequently (Wulfsberg 1989; Petersen 1998; Mardo 2008; Vero-Carbonell 2015; Lin 2016; Ramos 2016; EBF3-HADDS Foundation; Unique).

“ He has sensitive hearing. He hears everything – aeroplanes from inside the house, heaters turning on and off. ” – *2½ years*

Feet

23 months old with a 10q26.1 deletion

The feet of those with a 10q25/6 deletion are often not perfectly formed. Evidence from medical literature and Unique suggests that almost half of children have a foot anomaly. A number of children have joined toes (syndactyly), usually involving the second and third toes. Other anomalies include talipes (clubfoot); overlapping toes; flat feet; feet that turn inwards; hammer toes (where one or more toes is permanently bent); sandal gap (an increased gap between the first and second toe); and small feet. Some children who have clubfoot may need surgery to correct the unusual positioning of their feet, although for other children plaster and splints may be sufficient. Generally, the foot anomalies may mean that children require special insoles, inserts in their shoes or special supportive footwear (Lewandowski 1978; Wulfsberg 1989; Leonard 1999; Waggoner 1999; Irving 2003; Ramos 2016; Lacaria 2017; Lopes 2017; Lin 2021; EBF3-HADDS Foundation; Unique).

Hands

Many children with 10q25/6 deletions have unusual hands, including large hands; an incurving little finger (clinodactyly); single palmar crease; extra palmar crease; underdeveloped or concave nails; long or tapering fingers; or fingers that are fused together (syndactyly). In general, the hand anomalies do not greatly affect the function of the hands, although they can lead to problems with fine motor skills. A number of Unique children have high muscle tone (hypertonia) in their hands which can lead to problems with fine motor skills and make using sign language more challenging. One Unique child has no finger pads and one has stiff joints in her hands and can no longer make a ‘fist’ (Mehta 1987; Wulfsberg 1989; Petit 1998; Waggoner 1999; Lukusa 2002; Irving 2003; Scigliano 2004; Motoyama 2008; Lin 2016; Ramos 2016; EBF3-HADDS Foundation; Unique).

Genital anomalies

Minor anomalies of the genitals are common in babies with chromosome disorders, including HADDS, most often affecting boys. The most common problem is cryptorchidism (undescended testes) which affects over 80 per cent of boys with a 10q25/6 deletion. The testicles can be brought down by a straightforward surgical operation if they do not descend of their own accord in time. Cases of micropenis (a small penis), anteriorly placed anus (the anus is further forwards than it should be) and an imperforate anus (a malformed, blind anus) have also been observed. Published medical literature reports ambiguous male genitalia in at least three boys

(including one with an interstitial deletion, one with a 10q25.13q26.3 deletion and one with a 10q25.3 deletion) and complete male to female sex reversal has been observed in at least two males (including one with a 10q25 deletion and one with a 10q26 deletion) (Mehta 1987; Wilkie 1993; Chung 1998; Tanabe 1999; Irving 2003; Mardo 2008; Yatsenko 2009; Piard 2014; Lin 2016; Ramos 2016; EBF3-HADDS Foundation; Unique).

Girls may also have minor genital anomalies, although these are much less common. The most frequent genital anomaly in girls is underdeveloped labia (Rooney 1989; Ogata 2000; Lin 2016; Ramos 2016; EBF3-HADDS Foundation; Unique).

9 years old with a 10q26.1 deletion

Palate

A cleft palate (opening in the roof of the mouth resulting from the palate not forming correctly during development) or high-arched palate has been reported to affect some children with a 10q25/6 deletion.

The evidence at Unique is that clefts affected 13 per cent (4/30) of those who participated in the 2009 Unique survey regardless of the breakpoint. Cleft palate has also been reported in a number of cases in published medical literature and is a feature of HADDS (Mulcahy 1982; Shapiro 1985; Petersen 1998; Scigliano 2004; Ramos 2016; EBF3-HADDS Foundation; Unique).

Both cleft and high palates can contribute to the early feeding difficulties seen in children. A cleft or high palate may also make speech more difficult.

Breathing

Breathing problems can affect children with 10q25/6 deletions and are a feature of HADDS. Around a third of all babies, regardless of the breakpoint, had respiratory distress at birth (see Newborn). Some babies need resuscitation or intubation at birth but subsequently manage to breathe normally, although some require ventilation for up to six months. At least seven Unique children had frequent respiratory tract infections, although several later outgrew them. At least five Unique children suffered from aspiration pneumonia, where there is inhalation of something e.g. food, liquid or vomit, from either the stomach or the oral airway leading to inflammation of the lungs. Asthma and severe bronchiolitis (inflammation of the small airways in the lungs) have also been reported (Scigliano 2004; EBF3-HADDS Foundation; Unique).

Teeth

Generally speaking, children with chromosome disorders appear to have somewhat more dental problems than their peers. A number of Unique children had teeth that were slow to erupt, whereas others acquired adult (permanent) teeth early. A few Unique children had deciduous (milk) teeth that lacked enamel and one child required regular dental cleaning due to excessive plaque build-up. A small minority

of children have a hypersensitive mouth (*see* Personality & Behaviours) resulting in an aversion to brushing teeth and visiting the dentist; at least one child requires a hospital visit for dental treatment. Dental over-crowding is a feature of HADDS (EBF3 -HADDS Foundation; Unique).

Spine

Anomalies of the spine are occasionally observed in those with a 10q25/26 deletion and are a feature of HADDS. A small proportion (around 20 per cent in the Unique survey) have scoliosis (a sideways curvature of the spine) or occasionally kyphosis (an outward curvature of the spine) or kyphoscoliosis. Underlying the curvature of the spine may be abnormalities of muscle tone, and in some cases the bones of the spine (vertebrae) may be fused together or incorrectly formed. Curvatures of the spine often develop or worsen with age and should be monitored carefully. The curvature can be treated with physiotherapy and exercises, or a support brace may be needed. If the curve becomes marked it may be necessary to undergo spinal fusion surgery and straighten the spine using rods, as was the experience of some Unique members.
Some babies are born with a tethered cord (the bottom of the spinal cord is usually free within the spinal column but occasionally it becomes attached (tethered) to one of the surrounding structures), which can be an underlying contributing factor for neurogenic bladder dysfunction (when a person lacks bladder control due to brain, spinal cord or nerve problems), which has been observed on occasion and may require catheterisation. A tethered cord can be treated with rest, physiotherapy and medications to help relieve symptoms, but untethering surgery may be the only permanent, successful treatment for more severe cases.
A few babies were born with a sacral dimple (a dimple or hole in the skin just above the crease between the buttocks). For one Unique child the fluid sac at the base of the spine was larger than is usual (Turleau 1979; Waggoner 1999; Lukusa and Fryns 2000; Lukusa 2002; Scigliano 2004; Piard 2014; EBF3-HADDS Foundation; Unique).

Digestion

One problem is chronic constipation which appears to have affected almost half of Unique children and is a feature of HADDS. Dietary changes and/or medication can help to manage the condition (Unique).

Other concerns

A broad chest with wide-spaced nipples has been reported in as many as 30 per cent of those with a 10q25/6 deletion (Wulfsberg 1989).

Both umbilical and inguinal hernias have also been reported in small number of people. A hernia is a lump that results from a part of the intestine slipping through a weakness in the abdominal wall. An umbilical hernia is a soft, skin-covered bulge at the belly button (umbilicus) that can look bigger when the baby strains or cries. The bulge contains a small piece of abdominal lining and sometimes part of the abdominal organs. It is caused by incomplete closure of the ring of muscle that the umbilical cord passed through in early life. An inguinal

4 years old with a 10q26.3 deletion

hernia, a bulge containing part of the bowel, is located in the lower abdomen (Petit 1998; Lukusa and Fryns 2002; Scigliano 2004).

Personality & Behaviours

Children with a 10q25/6 deletion are typically happy, sociable, loving and affectionate.

A number of families describe their children as particularly empathetic. However, a significant number of children – although not all – show a similar pattern of behavioural difficulties, including social, emotional and anxiety disorders, such as autism spectrum disorder (ASD); anxiety, attention deficit hyperactivity disorder (ADHD); sensory processing disorder (SPD); and obsessive compulsive disorder (OCD). One study reported behavioural issues in over half of those children with a 10q25/6 deletion and these concerns are known to be a feature of HADDS.

The behavioural issues can be wide-ranging and children may exhibit a combination of features. Babies and toddlers may demonstrate a lack of crying. Later, children may typically display sudden and extreme changes of behaviour, with outbursts of aggressiveness and destructive behaviour. This behaviour can be directed at themselves and others and include hair pulling, hitting, biting and kicking. A small minority have been known to be self-destructive or self-harm. They can be abusive, swearing at others. They are often easily frustrated and can be impulsive. They tend to be hyperactive with poor concentration, a short attention span and are easily distracted, all of which can make learning more challenging. Six of the 29 (21 per cent) who took part in the 2009 survey had been diagnosed with ADHD, which is characterised by restlessness and a short attention span, and subsequently a significant number of other parents have told us about an ADHD diagnosis. Those diagnosed with ADHD include children with interstitial deletions, deletions in 10q26.1 and 10q26.3. These concerns are known to be a feature of HADDS. Many families report that their children are overly affectionate and show inappropriate friendliness.

A small number of reports in medical literature suggest that behaviour can worsen in the pre-pubertal years. Behavioural management techniques have helped many families, but for some children medication has been shown to be the only effective treatment. Other strategies employed by families include a low sugar diet with no food dyes (*see* the Unique leaflet on Behaviour for further information) (Petit 1998; Lukusa and Fryns 2000; Irving 2003; Courtens 2006; Lin 2016; Ramos 2016; Lopes 2017; EBF3-HADDS Foundation; Unique).

Sensory issues affect some children. They may display tactile sensitivity, disliking the touch of certain objects or textures, and/or oral hypersensitivity. At least two Unique children have a heightened body awareness: one has a weighted blanket when asleep and wears a weighted vest for part of the day; the other wears a weighted bag at times. Around half of those surveyed had sensitive hearing and were hypersensitive to noise, although some children outgrew this. There are also descriptions in both published medical literature and at Unique of children who are unaware of danger (Schrander-Stumpel 1991; Petit 1998; Courtens 2006; Deisseroth 2022; EBF3-HADDS Foundation; Unique).

Over 50 per cent of those who took part in the Unique survey reported that their children had an increased tolerance to pain, often not noticing when they had been quite badly hurt (Unique). A high pain threshold is a feature of HADDS (Deisseroth 2022; EBF3-HADDS Foundation).

Additionally, behaviour within the autistic spectrum have been reported both in published medical literature and in a significant number of Unique children. Some children do not have a diagnosis of autistic spectrum disorder (ASD) but show some autistic tendencies or traits. The autistic tendencies that have been noted include failing to recognise social cues, rarely crying and repeating movements like head shaking or wringing their fingers (Ramos 2016; Lopes 2017; Deisseroth 2022; EBF3-HADDS Foundation; Unique).

❝ Everyone loves him. He has a great personality and loves to say 'Hi' and 'Bye' to everyone. He is very easygoing and rarely cries. ❞ – *2½ years*

❝ He has a warm heart and is warm and funny. ❞ – *3 years*

❝ She is not a particularly naughty child and has no challenging behaviour. She has on one occasion shown inappropriate friendliness to a stranger in the park, so this needs watching. She is sometimes shy in new situations and can be quite clingy. ❞ – 4 years

❝ She works hard for everything and is determined. ❞ – *4 years*

❝ She has been diagnosed with sensory issues, including auditory sensitivity, oral seeking and sensitivity, and she has problems regulating sensory input. She has also been diagnosed with obsessive compulsive disorder (OCD) and autism. She doesn't like to see anyone hurt and loves to share. ❞ – *5 years*

❝ She has challenging behaviour and can be difficult when tired. She has ADHD and is unable to sit and focus for a period of time at school. ❞ – *7 years*

❝ She has just started to be disruptive at school. ❞ – 7½ *years*

❝ She is a very lovely little person. She loves all the family and she is permanently telling them so! She is very sociable and likes to say 'Hello' to everybody. – 8½ years

❝ He is very social and likes to be with his friends. He picks (almost compulsively) at threads (on the hem of a T-shirt or socks). ❞ – *9 years*

❝ He is always happy and everyone loves his cheerful character. He can be impulsive and likes to get his own way. ❞ – *9 years*

❝ Her behaviour was unusually calm until 2½ years and then was very difficult (agitated, always in opposition, always testing the limits) until 6 years. It is now much better. She shows inappropriate friendliness with adults she doesn't know. – 10 years

❝ She is very affectionate and caring. ❞ – *10 years*

❝ Her behaviour is quite abusive. She swears, bites, pinches and back chats. But she is loving all of the time. ❞ – *11 years*

❝ He is extremely social and is very loving and emotional. ❞ – *20 years*

Sleep

The majority of children go to bed easily at bedtime and sleep well, but sleep problems affect some children. Some children find it hard to settle at bedtime and consequently fall asleep late, which may mean they struggle to get up in the morning and are tired the next day. Others seem to have a diminished need for sleep, sometimes only needing six hours per night. Some children have episodes of sleep

apnoea (when a person's breathing is interrupted during sleep), which should be investigated (Mehta 1987; Lacaria 2017; EBF3-HADDS Foundation; Unique) (*see* the Unique leaflet on Sleep for further information).

> " He is difficult to settle when he is tired and can take up to an hour or more to settle at bedtime and will cry for no reason. " – 2 years

> " Bedtimes are tricky as she only settles well about seven days per month. Often it is 11pm before she goes to sleep and then she is so tired at school the next day. " – 7½ years

6 months

14 months

4 years

Growing up with a 10q26.1 deletion

Puberty and Fertility

There is limited information available on puberty in both males and females with 10q25/6 deletions. The evidence at Unique is that puberty proceeds as normal within the usual age range, although puberty began early, at 8 years of age, for one girl. For some children, hypotonia progresses to hypertonia, which means muscles and joints tighten and walking can become more difficult and tiring. Urinary issues may also emerge at this stage (EBF3-HADDS Foundation; Unique).

19 years old with a 10q25.2q26.11 deletion

There are several cases in medical literature of a familial 10q deletion. One family has six members with the deletion, ranging in age from 3 years to 63 years. A 63-year-old woman passed the deletion on to three daughters, one of whom passed the deletion on to a son and a daughter. Another family consisted of a 40-year-old woman who passed a 10q26.2 deletion on to a 9-year-old daughter.

At least 8 Unique members had inherited a deletion from their father or mother, five with a deletion involving only 10p26.3 and individual cases involving 10q26.2/26.3, 10q 25.2 and 10q25.1 (Irving 2003; Unique).

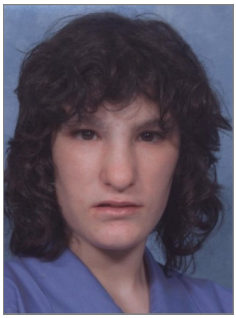
Adults with a 10q25/6 deletion

In 2009, Unique had seven adult members between the ages of 18 and 28 years; by 2021, the number of adult members had risen to over 60. We know that a 20-year-old man with an interstitial deletion had moderate to severe learning difficulties, ADHD and spoke in two to three word sentences. He walked on his toes but did trampolining, swimming and dancing. He was friendly and very active and lived in a group home with five others. An 18-year-old girl with a 10q26 deletion had left a special educational school within the previous year. She learned to read around the age of five years. She had ADHD and challenging behaviour, but loved books, children's TV shows and arts and crafts. She lived at home with her family and needed support when out and about. She went to a day centre for some days a week and did supported voluntary work. A 23-year-old woman with a 10q26.1 deletion left school at 16 years of age and could read and write. She loved music, reading magazines and doing word-search puzzles and had basic computer literacy. She was diagnosed with ADHD and was living in a low security hospital due to her challenging behaviour. A 23-year-old woman with a 10q26.3 deletion had learning difficulties. She was able to drive and help out on the farm where she lived.

A 36-year-old woman with a 10q26.2q26.3 deletion had lived in a housing project for adults with learning difficulties since she was 21 years old. She had a number of health concerns that had worsened over time and had a care-worker in the afternoons and saw a social worker once a fortnight. A 19-year-old woman with a 10q26.3 deletion had no serious health concerns and lived in an institution for learning-disabled people during the week. She particularly enjoyed the clear programme of activities this setting provided.

6 months

6 years old, far right with her brother and sister



18 years

Growing up with a 10q26 deletion

A number of adults have been reported in published medical literature. One family had six members with a 10q26.2 terminal deletion with the oldest, 63 years old, who attended mainstream school and worked as a supermarket shelf-stacker. She passed the deletion on to three daughters. One daughter, 38 years old at the time of the report, attended mainstream school but did not achieve any examinations and worked in a food factory and supervised junior staff. The second daughter (37 years old) attended mainstream school and worked in a factory as a packer; she had no behavioural issues but was said to be accident-prone and sustained a number of fractures. The third daughter (19 years old) had moderate learning difficulties and attended a special school. Her behaviour was occasionally disruptive and she was described as being very active. A 40-year-old woman, who passed the 10q26.2 deletion on to a daughter, left school without obtaining any examinations and worked in catering. A 48-year-old man has severe learning problems and short stature (McCandless 2000; Irving 2003).

Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why a 10q25/6 deletion has occurred. In the majority of cases a 10q25/6 deletion occurs when both parents have unaffected chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 10q25 and 10q26 deletions are caused by a change that occurred when the parents' sperm or egg cells formed or possibly during formation and copying of the early cells after the egg and sperm joined. Rarely, a 10q25/26 deletion is inherited from a similarly affected parent.

Some 10q25 and 10q26 deletions are accompanied by a gain of material from another chromosome and are often the result of a rearrangement in one parent's chromosomes. This is usually a rearrangement known as a balanced translocation in which material has swapped places between chromosomes. As no genetically important material has been lost or gained, the parent usually has no clinical or developmental problems, although they may have difficulties with fertility or childbearing. Balanced translocations involving one or more chromosomes are not rare: one person in 500 has one, making a total world population of over 13 million balanced translocation carriers (*see* the Unique leaflet on Balanced Translocations for further information).

Whether the deletion is inherited or *de novo*, what is certain is that as a parent there is nothing you did to cause the 10q25/6 deletion 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?

The possibility of having another pregnancy with a 10q25/6 deletion depends on the parents' chromosomes. If both parents have unaffected chromosomes when their blood cells are tested, the deletion is very unlikely to happen again in a subsequent pregnancy. Very rarely (less than 1% (1 in 100)), both parents have unaffected chromosomes by a blood test, but a few of their egg or sperm cells carry a chromosomal change. This is called germline mosaicism and it means that parents whose chromosomes appear unaffected when their blood is tested can have more than one child with the deletion.

However, if either parent has a chromosome rearrangement or deletion involving 10q25 or 10q26, the possibility is greatly increased of having other affected pregnancies.

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.

Ongoing research involving 10q25/6

The size of the deleted region found in those with 10q25/6 deletions varies widely, ranging from small interstitial deletions to much larger deletions, and may include an individual gene or multiple genes. There is also a wide variation in the observed features, even within families where the same deletion is shared. The features associated with a 10q25/26 deletion are likely to depend on the genetic material involved and, more specifically, which genes and/or regions that control genes are missing, as well as numerous other factors that we are only just beginning to understand. Nonetheless, there have been attempts to try to correlate the size of the 10q25/6 deletion with the range and severity of features, but no strong correlation has been found (Vera-Carbonell 2015; Tanteles 2015; Faria 2016; Lacaria 2017; Li 2020).

However, the increasing use of molecular techniques such as array-CGH in the research laboratory has enabled more accurate definition of the breakpoints involved in 10q25/26 deletions. This, in turn, has enabled researchers to study more accurately which parts of the chromosome are missing and attempt to correlate certain regions with the different clinical features of the condition. Indeed, a number of studies have attempted to correlate the clinical features in people with a 10q deletion with the part of the chromosome they have missing in order to define a critical region(s) of 10q that is responsible for the features of 10q deletions, and to help to narrow down the regions and/or genes responsible. Nonetheless, the precise relationship between causative genes and the features observed remain unclear and further research is needed. For example, evidence suggests that deletions with a breakpoint in band 10q25.3 are associated with more significant genital anomalies in boys than deletions with a more distal breakpoint in 10q26.12 or 10q26.13, and it has been suggested that multiple genes in 10q25q26 play a role in genital development (see details below) (Wulfsberg 1989; Petersen 1998; Irving 2003; Courtens 2006; Bagheri-Fam 2008; Yatsenko 2009; Piard 2014; Choucair 2015; Ramos 2016; Vera-Carbonell 2015; Tanteles 2015; Faria 2016; Lacaria 2017; Li 2020; Sutani 2020; Neocleous 2020; Nishi 2021; Deisseroth 2022; Unique).

Genes

While new information is constantly emerging that will help us further understand the role of genes in 10q25q26 deletions, the possible role of a few of the genes within 10q25q26 include:

EBF3 (EBF Transcription Factor 3)
Location: 10q26.3
[*129,835,233-129,973,053* (GRCh38/hg38)]
[*131,633,497-131,762,538* (GRCh37/hg19)]

The strong overlap in features between 10q26 deletion syndrome and HADDS points to deletion of the *EBF3* gene as the main causative gene for the features of 10q26 deletion syndrome. The similarities in features in individuals with both small and much larger 10q26 terminal deletions including *EBF3* also points to the crucial role this gene plays (Lopes 2017; Deisseroth 2020; EBF3-HADDS Foundation) (*see* Hypotonia, Ataxia and Delayed Development Syndrome (HADDS)).

FGFR2 (fibroblast growth factor receptor 2)
Location: 10q26.13
[121,478,330-121,598,458 (GRCh38/hg38)]
[123,237,844-123,357,972 (GRCh37/hg19)]

The *FGFR2* gene is associated with a number of diseases, including Pfeiffer Syndrome and Crouzon Syndrome. It has also been proposed that deletion of *FGFR2* is behind the characteristic facial features associated with 10q26 deletion syndrome. *FGFR2* is highly expressed during embryonic development in tissues associated with the developing genitalia and it has been suggested that it may also be one of a number of genes that may have a role in the genital anomalies associated with 10q26 deletion syndrome (Bagheri-Fam 2008; Gredler 2015; Choucair 2015; Vera-Carbonell 2015; Faria 2016; Li 2020; Sutani 2020).

EMX2 (empty spiracles homeobox 2)
Location: 10q26.11
[117,542,445-117,549,546 (GRCh38/hg38)]
[119,302,257-119,309,057 (GRCh37/hg19)]

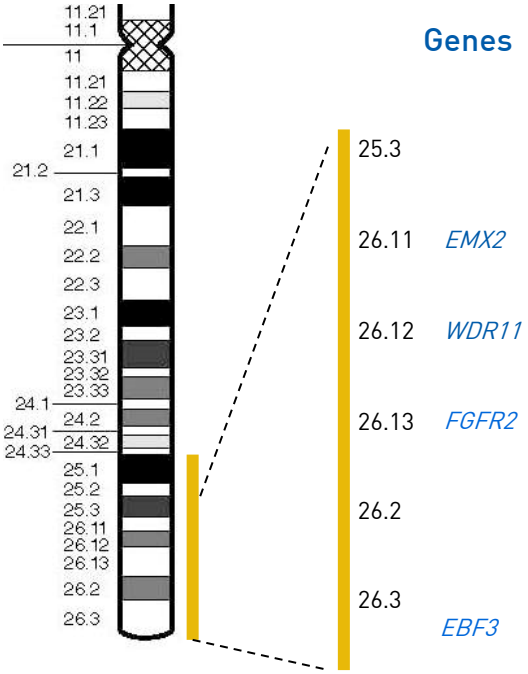
The *EMX2* gene has been shown to be critical for central nervous system and urogenital function. Mice that are missing this gene show a complete absence of kidneys, ureters, gonads and genital tracts. Having only one functional copy of the *EMX2* gene is thought to be one of the causes of genital anomalies associated with 10q25q26 deletions and has been suggested to be responsible for the disorders of sex development that are occasionally observed (Irving 2003; Mardo 2008; Piard 2014; Cahoucair 2015; Ramos 2016).

WDR11 (WD Repeat Domain 11)
Location: 10q26.12
[120,851,305-120,909,525 (GRCh38/hg38)]
[122,610,874-122,669,036 (GRCh37/hg19)]

The *WDR11* gene is associated with several diseases, including Kallmann syndrome and congenital hypogonadotropic hypogonadism. It has subsequently been proposed

that deletion of the *WDR11* gene may also have a role in the anomalies of the heart, growth retardation and coloboma associated with 10q26 deletion syndrome (Choucair 2015; Neocleous 2020; Li 2020; Sutani 2020).

It is important to remember that while identifying the gene(s) responsible for certain features associated with 10q deletions is interesting and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene(s) is missing 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.



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Inform Network Support

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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/donate
Please help us to help you!

www.hadds.org/ - The EBF3-HADDS Foundation was created to promote awareness, research and support for a rare genetic syndrome discovered in 2016

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