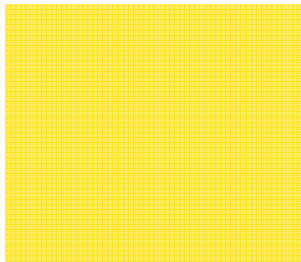


Unique

2q37 deletions



Sources

The information in this leaflet comes from the medical literature and from Unique's members with 2q37 deletions, who were surveyed in 2003. When the leaflet was published, Unique had 40 members with a 2q37 deletion. Unique is very grateful to the families who completed the survey.

References

For references from the medical literature, the first-named author and publication date are given to allow you to look for abstracts or original articles on the internet in PubMed. You can also obtain abstracts and articles from Unique. References to information from Unique are marked U.

2q37 deletions

2q37 deletion syndrome is an emerging chromosome condition. People with the syndrome have lost a small amount of genetic material (DNA) from the end of one of their two chromosome 2s and this affects their development. However, exact breakpoints vary and even when they are the same, a striking variability is a hallmark of 2q37 deletion syndrome. Even family members with exactly the same amount of lost chromosome material can be very differently affected, although the effects of the syndrome are usually seen in the same areas of development. In this chromosome condition more than in many others, the individual's other genes, their personality, home environment and the opportunities and experiences offered to them will help to shape their future development, needs and achievements (Batstone 2003; Aldred 2004; U).

Most people with 2q37 deletions have lost the genetic material from every cell in their body. A few have only lost it in a proportion of their cells. This is called mosaicism and generally lessens the impact of the condition.

Frequent features

These features have been found to be common in a group of people with a 2q37 deletion. An individual child may or may not be affected.

- Developmental delay.
- A degree of learning disability, usually mild or moderate.
- Hypotonia (low muscle tone, floppiness) in babyhood and sometimes in early childhood.
- Short hands and feet. The bones in the hands and feet are short, and when the hand is made into a fist, there can be a dimple where you expect to see a knuckle. The 4th and sometimes 3rd and 5th fingers are often short. This resembles a genetic condition known as Albright's hereditary osteodystrophy (AHO, see page 9). Some children have unusual spacing between the fingers and toes, short arms and legs or slim, tapering fingers.
- Growth delay.
- Tendency to put on weight by middle childhood.
- Eczema.
- Hernias, especially umbilical and inguinal (in the groin).
- Behaviour difficulties, including autism.
- Heart conditions affect one child in five.

(Lin 1992; Conrad 1995; Rauch 1996; Viot-Szoboszalai 1998; Reddy 1999; Aldred 2004; U)

Does the breakpoint matter?

The point where the chromosome breaks in people with 2q37 deletions varies between bands 2q37.1, 2 and 3. A recent search found no common breakpoints, suggesting that there are no sites at the end of 2q that are particularly fragile. This means that different sized pieces of chromosome are missing. However, the amount of material missing does not appear to determine the severity of the clinical difficulties. Researchers and *Unique* have found that people with a large deletion can be more mildly affected than those with a small deletion from 2q37.3. This means that other factors must affect the development of 2q37 deletion syndrome but what these factors are is not yet known (Aldred 2004).

In many people with a 2q37 deletion, material has been lost or gained from another chromosome as well. This is almost bound to alter the overall picture for the individual. Contact *Unique* for details of other karyotypes (chromosome make-ups). Researchers are looking for the gene or genes that cause the AHO-like symptoms (see page 9) and have recently narrowed their search to a 3 megabase segment, that is, 3 million DNA base pairs ('rungs' on the DNA ladder). There are currently several candidate genes, known as *GPC1*, *HDLBP* and *STK25*.

Why did this happen?

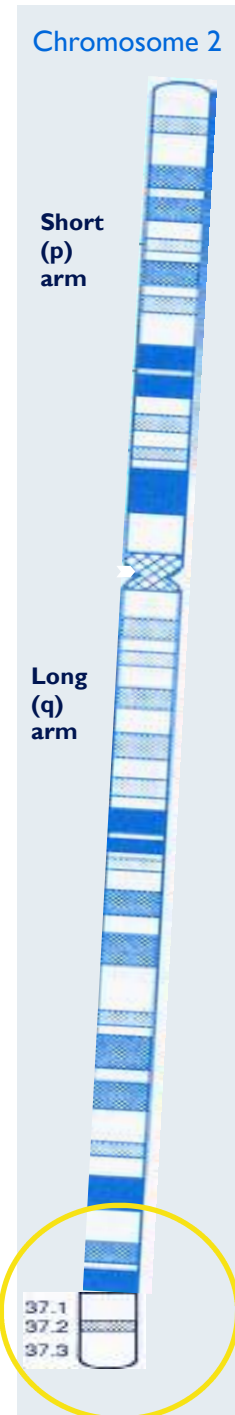
To answer this question, the parents' chromosomes need to be examined, using the same tests used to detect the rearrangement in the child.

In most families, both parents have normal chromosomes. The 2q37 deletion has then happened as a one-off event and it is very unlikely that any future children will be affected.

Geneticists call this *de novo*, meaning that the child with the chromosome disorder is the only person in the family known to be affected and it has not been inherited. A *de novo* deletion has usually occurred during the formation of the egg or the sperm. Chromosome rearrangements happen as a natural part of evolution and nothing that either parent did caused it to happen or could have prevented it.

In a few families, one parent has a structural rearrangement of their own chromosomes. This is usually balanced so that all the genes and chromosome material are present and the parents are healthy. However, in these families the risk of having another affected child is higher.

Your genetics service can offer you an appointment to discuss this when you are thinking about another pregnancy.



Growth

Unique records show that babies grow fairly well before birth and are usually born at term, their weight ranging from 4lb 10oz (2100g) to 9lb 11oz (4400 g). Research reports show that after birth two-thirds of babies and children may put on weight and grow at the rate of other children while around one child in three grows more slowly and is short compared with the rest of their family. *Unique* records suggest that many families can expect their child to be short. Out of 12 children with a height record, only one is above average height. One adult is 4' 6" tall (1.37 metres). One child has been treated with growth hormone but has not yet entered puberty, so it is too early to know final adult height. Too few children with 2q deletions have tried growth hormone for the outcome to be known, and evidence from studies in other chromosome conditions is conflicting.

Many research reports suggest that the typical build of a child with a 2q37 deletion is stocky. This is not the experience of *Unique*; 50 per cent of surveyed members stated specifically that their child was thin or petite (Bijlsma 1999; Reddy 1999; U).

Food and eating

Babies with a 2q37 deletion typically have low muscle tone which can affect their ability to suck. In addition, they may find it hard to co-ordinate sucking and swallowing. From a practical point of view, this means that feeds by breast or bottle can take a very long time. There are many ways to help a baby who is having difficulty feeding and if necessary it is possible to feed temporarily by nasogastric tube or through a gastrostomy tube direct into the stomach to ensure that a baby gets enough nutrients.

Gastro oesophageal reflux (when milk flushes back from the stomach up the food pipe) and vomiting are also common and babies who inhale milk are at risk of aspiration pneumonia. Careful feeding and positioning can help reflux as can feed thickeners and prescribed medication to inhibit gastric acid. If simple measures are not enough, it is possible to cure reflux with a surgical operation known as a fundoplication, in which the action of the valve between the food pipe and the stomach is improved.

The tendency to choke means that babies may move late to solids, and some may benefit from fortified or adapted milks to meet their extra nutritional needs after six months. A wide range of finger foods and nutritious drinks is needed until children learn to handle a spoon. Some children use cutlery when you would expect, but others only develop enough dexterity by the age of four or five. Constipation may occur and it can be severe, so if the simple remedies of additional fluid, fibre and exercise are not successful, families should seek medical advice promptly. An additional issue is a tendency for children past babyhood to become overweight. While overeating occurs in other chromosome conditions and may in part be attributed to a lack of a sense of fullness, in children with 2q37 deletions it may be linked with AHO (see page 9) (Conrad 1995; Smith 2001; U).

Learning

Children are very likely to need some support with their learning, although the extent varies widely between individuals even with the same 2q37 deletion and within the same family. Many research reports suggest that delay is no more than mild to moderate. However, there is almost no detailed information (Lin 1992; Conrad 1995; Grammatico 1999; Giardino 2001; U).

Evidence from 21 *Unique* families showed a scattered pattern, with great variation in the skills that young people achieved. Seven children were considered to have mild difficulties, in two they were moderate and twelve families described the level of learning disability as severe. One adult had a borderline profound learning disability.

Among those with a **mild learning disability**, a 20-year-old only showed difficulties with understanding and short term memory; a 14-year-old was one to two years behind the curriculum in mathematics and reading; a nine-year-old started to read and write at the age of 7.

“ Very variable profile, with excellent verbal skills and other areas varying from very poor to average. She is a couple of years behind educationally in many areas. Her reading and writing have come on very well since age seven. She struggles at school with getting tired, immaturity, her inability to follow instructions easily or to initiate work on her own. She also has a very poor sense of direction - age 8

“ Although her IQ is within normal limits, she has sensory integration disorder. Her memory is very good, and although she knows the vowel and consonant sounds, she has difficulty in sounding out words. Her maths skills are at kindergarten level, her writing is age appropriate but she needs considerable help to do expressive or creative writing - age 8

The two children with a **moderate learning disability** both showed a facility for music. One additionally had good attention skills.

“ He has a good memory and he is quite good at humming nursery rhymes. If I teach or show him something a couple of times he will remember it - age 4

Among the twelve children with a **severe learning disability**, there was more evidence of a scatter of skills. Three children had difficulty concentrating in a group environment.

“ She has no speech, reading or writing. She is now doing very well at a residential college learning life and living skill - age 19

“ Officially he cannot read but outside school he recognises words like exit and shop names. He is still practising writing his name. Has a very short attention span. I think he could do much more at school and worry that his teachers have unfairly low expectation - age 10

“ Achieving middle preparatory grades for the UK national curriculum. Variable earlier performance with some aspects on target and others behind - age 6

“ His learning is severely affected by autism. He has extremely sensitive hearing and is bothered by background noise - age 4

Speech and communication

Most children learn to talk, but speech develops late. The average age at which Unique children spoke their first words was almost three years (range 18 months to 6½ years). Apart from one child whose vocal cords did not oppose correctly, the delay could not be explained by physical causes. On the contrary, there was an evident association between learning ability and speech development. For some children there was also a reluctance to communicate, linked with autistic traits.

Before learning to speak, children used gestures and vocal noises. They showed a variable degree of success with signing systems. For some, signing unlocked the gates to communication, while others never mastered it and moved directly to speech. Understanding was usually ahead of expression. Frustration at their inability to communicate was all too obvious: children would shout, cry, headbutt, hit or bite themselves or throw themselves to the floor.

- “ She uses Makaton and her own signs as well as a talker. She understands everything - age 19*
- “ He uses complex sentences and Makaton but his subject matter is repetitive - age 15*
- “ Her speech is good, she uses long and complex sentences though she has some grammar problems - age 14*
- “ Is it the cocktail party syndrome? He speaks in long, complex and rambling sentences – though if the words are too hard to organise he stutters or gives up half way. He has problems understanding long complex speech and walks away from some videos, preferring speech that is short and repetitive - age 10*
- “ Her verbal skills are excellent and she uses complex sentences. But she has a very uneven profile and while her expressive language is good her understanding is poor and her gestures are sometimes rather strange - age 8*
- “ He didn't pick Makaton up but he is now picking up words from adults and repeating them later. Most of his sentences are instructions but he also now talks about his day when asked. His sounds are unclear and he appears to use his throat to speak, not his tongue - age 6*
- “ He has shown an ability to use picture exchange cards recently after having nutritional supplements including B vitamins and music therapy. Otherwise he cries or uses eye gaze. He tries to say dad, bath, apple, banana. We are realising that he understands a lot more than we thought - age 4*
- “ His language seems to come and go. He used to have 5 to 8 words, right now he has none or one - age 3*

This story shows how vital it is to fully investigate the communication aspects. A girl with a 2q37.3 deletion appeared developmentally delayed. Her parents had noticed a lack of eye contact in babyhood. She was speaking some words at the age of 4 but by 5 her response to others' social or verbal overtures was limited. Testing at school showed learning disability. At the age of 13, she learned to type with one finger. She can now type complex, grammatically correct sentences – something she has never achieved through speech. By typing her answers she achieved a score of 107 on a verbal reasoning test and became a college student (Smith 2001).

Mobility and activity

Research reports show that most children will be delayed in reaching their developmental milestones, but they will get there in the end and some children will experience no motor delay (Conrad 1995; Reddy 1999; U).

Low muscle tone (hypotonia, which shows as a floppiness as though the baby or child is profoundly relaxed) is extremely common but improves with maturity, practice and physiotherapy (physical therapy). Most *Unique* children are mildly affected, needing physiotherapy in the pre-school years only. However, two families reported severe hypotonia. Both children were still under 5, but neither was walking yet. Once children are on the move, balance and fatigue remain ongoing issues.

On average *Unique* babies rolled at 8 months (range 3 to 14 months). They sat up at 10 months (range 4 months to 18 months), although one child only sat at the age of four and a half years. Crawling, a stage that may be by-passed in children with a chromosome disorder, was common among *Unique* babies who acquired the skill on average by the age of 16 months (range 10 to 26 months). Children took their first steps on average by two and a half years although there was a really wide range from 19 months to four and a half years. Some children benefited from using a stander or walker frame.

Once walking, children may lack a sense of danger and need help over uneven ground. Their gait can be unusual and they may be late in learning other mobility skills like running, hopping and skipping. When running, they may tend to hold their arms out to keep balance but even so, they fall much more often than other children and need a safe play environment and an adult hand available when out walking.

Swimming is an important and helpful activity, as is well-supervised playground play, dancing and riding for the disabled. Despite initial delays, one 8-year-old was swimming, playing soccer, doing gymnastics, cycling and roller skating. More typically, perhaps, a 15-year-old was mastering a 2-wheeler and swimming a few strokes unaided (Reddy 1999; U).

Lax joints

Extremely lax joints can affect more than half of all children with a 2q37 deletion. Two *Unique* children have hyperflexible fingers. Congenital dislocation of the hip and coxa valga (outward-turning of the hips) have also been noted, as has a particular style of tilting walk that relates to a weakness of the hip. Four out of 26 *Unique* girls (15 per cent) were affected: in two girls the hips were corrected with splinting, but one girl needed surgery at eight months (Wilson 1995; Aldred 2004; U).

Spinal curvature

Scoliosis (a sideways curve), kyphosis (a backward curve, creating a hump) and lordosis (an inward curve) may all occur. In the three affected *Unique* children, one is a child who is still not walking at the age of 4, in another 4-year-old increased mobility has started to correct the curve and in the third it is very slight (U).

Medical concerns

Most children with 2q37 deletion syndrome do not have serious medical problems. All the same, the features of the syndrome vary widely, so medical conditions can occur. The conditions are listed below in approximate order of frequency.

■ **Kidney and urinary tract**

Nine *Unique* children (24 per cent) have a kidney anomaly or have had a urinary tract infection. The six kidney anomalies were all minor and many came to light during routine ultrasound screening. One child had a single kidney and in another, one kidney was malpositioned in the middle of the abdomen. Three children had a horseshoe kidney. One child had urinary reflux, a condition in which some urine returns to the kidneys rather than passing out to the bladder.

Wilms' tumour is a type of kidney cancer that can occur in children with a 2q37 deletion, so a regular ultrasound scan of the renal and urinary system is usually offered until the age of eight. No *Unique* children developed Wilms' tumour (Conrad 1995; U).

■ **Hernias**

Inguinal hernias (part of the intestine bulges from the abdomen into a sac near the scrotum or the vagina) and umbilical hernias (part of the abdomen bulges out through the umbilical ring at the navel) are particularly common, but diaphragmatic hernias (there is a hole in the muscular sheet dividing the abdomen from the chest, allowing the contents of the abdomen to amass in the chest and take up space needed by the growing lungs) also occur. Umbilical hernias can be minor and self-heal in time. This was the case for three affected *Unique* children. However, diaphragmatic hernias and inguinal hernias need surgical correction.

■ **Heart conditions**

All babies with a known 2q37 deletion will have a careful cardiac examination as a small number have been reported to have a congenital heart condition. The range of conditions is broad – holes in the heart (atrial and ventricular septal defects), persistent ductus arteriosus and patent foramen ovale (both persisting structures of the fetal heart), coarctation (narrowing) of the aorta and a bicuspid valve (the valve that regulates blood flow from the left ventricle into the aorta has only two instead of three flaps or valves). While some conditions resolve naturally with time, a few babies will need surgery. In the *Unique* series, all six children with a heart condition are now thriving either after outgrowing the condition or after surgery (Conrad 1995; U).

■ **Childhood infections**

Coughs, colds and ear infections occur frequently in children with a 2q37 deletion as in other chromosome conditions. Ear and chest infections were common, attributed variously to weak chest muscles, tracheomalacia (unusually floppy airways) and to aspiration pneumonia, a possible consequence of severe gastro oesophageal reflux (Conrad 1995; Bijlsma 1999; U).

“ Ear infections were frequent as an infant and grommets and adenoid-tonsillectomy were offered but what we believe really helped was cranial osteopathy.

■ **Intestinal conditions**

Intestinal conditions have been found in a small number of children. Two had pyloric stenosis (the passage between the stomach and the small intestine narrows so that milk and food cannot get through), others had an obstruction of the intestines and in two further children the intestines were incorrectly sited within the abdomen. All these conditions can be corrected with surgery (Reddy 1999; U).

■ **Seizures**

Including febrile convulsions, seizures affected 17 to 35 per cent of children in the research reports. Among *Unique* members, seizures occurred in only three children: in one girl they started at 23 months and ceased by the age of 10 and two other children had febrile convulsions under school age. Evidence from imaging children's brains has shown that slightly enlarged ventricles may occur. There have also been isolated instances of hydrocephalus, excessive cerebrospinal fluid within the brain (Lin 1992; Conrad 1995; Phelan 1995; Reddy 1999; Aldred 2004; U).

■ **Genitals**

Minor genital anomalies have been found in around one child in 10. In boys, these have included a very small penis, small or undescended testicles. In girls the ovaries or uterus may be affected. Two boys in *Unique* had undescended testicles, both corrected with surgery (Conrad 1995; Viot-Szoboszlai 1998; Reddy 1999; U).

■ **Hearing**

Nine per cent of children investigated by researchers have some degree of hearing loss. At least two children had permanent sensorineural deafness, another had poor auditory discrimination and one child had very small ear canals, affecting hearing (Conrad 1995; Phelan 1995; U).

■ **Vision**

The most consistent feature was strabismus (squint), noted by 16 per cent of *Unique* members. One child had nystagmus and difficulty synchronising the movements of his eyes. Additionally, two children in research reports had a hooded upper eyelid, known as ptosis. Both ptosis and strabismus can be corrected (Batstone 2003; U).

■ **Albright's hereditary osteodystrophy (AHO)**

AHO is a genetic condition that affects the way that calcium is laid down in the skeleton. People with AHO have subtle physical changes including short stature, a round face and a tendency to put on too much weight. Some bones in the hands and feet are unusually short and some people have small hard lumps under the skin. They can also experience a range of hormonal problems. Most people with 'classical' AHO do not have a 2q37 deletion. Instead, they have low levels of a protein (Gs-alpha) directed by a gene on chromosome 20. Up to 50 per cent of people with a 2q37 deletion have unusual hands and feet, very similar to people with AHO, but they do not have any problem with their Gs-alpha gene. This shows that other genes found at 2q37.3, perhaps glypican-1 or vigilin, must also be important for skeletal development (Wilson 1995; Smith 2001).

People with 2q37 deletion and AHO-like hands or feet usually do not have any hard lumps under the skin or the hormone problems caused by Gs-alpha deficiency.

Behaviour

Many children with 2q37 deletions do develop some kind of behavioural disorder. In the largest series of 35 people, eleven (31 per cent) were known to have shown a variety of symptoms that included poor communication, repetitive behaviour, hyperactivity, rocking and head banging, twitches, facial contortions, autism and attention deficit disorder. The high rate of behaviour disorder means that families should have access to behaviour management support (Aldred 2004).

Link to *Unique's* Behaviour Management leaflet

Autism

Nine people with a 2q37 deletion and autism have been fully described and autism or repetitive, hyperactive behaviour was noted in 35 per cent of children in a recent survey (Smith 2001; Aldred 2004). Seventeen *Unique* families (46 per cent) said their child had autistic features. Leaving out pre-school children, the rate rose to 64 per cent. Familiar types of behaviour include limited eye and social contact, repetitive behaviour such as rocking, especially under stress, exclusive focus on certain toys or objects, extreme need for predictable routines, inability to express emotional thoughts or to interact emotionally, fear of the unpredictable and, finally, distress expressed as self injury. In some children, autistic features exist alongside a social, loving and contact-loving personality.

Families say repeatedly that autism undermines their child's development more than other symptoms of the chromosome deletion. Given the frequency at which it occurs and the possible improvements from early intervention, *Unique* believes that all children with a 2q37 deletion should be screened for autism.

Experience within *Unique* shows that the extent of the deletion is irrelevant to the development of autism. Children with deletions at 2q37.3 were just as likely to develop autism as children with a larger deletion. This observation agreed with the early evidence suggesting a possible site for an autism susceptibility gene at 2q37.3 (Aldred 2004; U).

These snapshots reflect some families' experiences.

" He is very social but has language delay and no interest in things (except balls). First signs noticed age 2 - age 3.

" We noticed the limited eye contact and social interactions at 9 months. Eye contact has improved but is still limited. Rocking has reduced as she develops more ways to play and now she just appears to rock in situations she is unsure of - age 4.

" Very severely affected. We have tried sensory integration, special education, nutritional supplements, hippotherapy and music therapy. He responds well to those who try to get to know him and love him and loves hugs and affection at most times and has a keen sense of knowing who is loving or judging of him. But by nature he is an introvert in that he needs time alone every day and sometimes only wants to be alone - age 4.

" She is very repetitive, however she is also very social and likes to be touched - age 5.

" Our real concern is over her social skills and inappropriate social responses for which she has training and needs constant behaviour modification. She also focuses on single objects such as the vacuum cleaner. She was diagnosed with autism at the age of 3 but the diagnosis was removed at 5. Adderall (dexamfetamine) for school helps a lot - age 8.

- “ We first noticed when she was 2 and didn’t respond to her name. She needs explicit information and instructions and doesn’t always understand if they are not. She is very immature and has no friends her own age but overall is only mildly affected - age 8.
- “ First noticed at 2, autism was diagnosed at 4. It has affected him in all areas of his life but in the past 18 months he has got better able to understand his own needs and know he can move away from people or change activities. The treatment has been to stick to routine and responses but more importantly to listen to him! - age 15.
- “ From a tiny baby we noticed she avoided eye contact and had attacks that we didn’t then recognise as panic. She has become more tolerant of new situations and so panics less but her self injury has become worse - age 18.

Managing behaviour

Families of children with a 2q37 deletion may face a range of extreme behaviours. There is no one personality type attributable to this chromosome condition, and many aspects are well known to any parent of a small child. However, the behaviours are more intense, more extreme, they last longer and parents need extra ingenuity and energy to cope with them.

Here are some examples of behaviour problems and solutions:

- *Ignoring instructions, continuing to do what she wants. What works? Trying to be consistent – age 4.*
- *Spitting on anything shiny or windows. Time out has reduced though not eliminated this - age 4.*
- *Grabbing other children in his excitement. Distraction worked, as telling him not to had the opposite effect and he enjoyed the attention - age 6.*
- *She gets frustrated when she can’t have things. Keep explanations simple, use time out for tantrums, lie if necessary! – age 8.*
- *Can show temper and lash out unpredictably as well as getting frightened by the unknown. Now his speech has improved he can be reasoned with when having a tantrum or, even better, defused by distraction – age 10.*
- *Extreme anxiety. Fluoxetine - age 10.*

Might a child with 2q37 syndrome ever be able to live independently?

2q37 deletion syndrome affects children in highly variable ways. Children who are mildly affected may well be able to lead high-quality independent adult lives. As important as the deletion are the child’s development, personality and any clinical difficulties. However, there is very limited experience. *Unique’s* oldest member is only in their twenties and currently at college learning life skills.

As far as personal care goes, toilet training is delayed although the age at which children become dry and clean is highly individual. Most *Unique* members were dry in the daytime by school age. A few teenagers were not reliably clean or dry at night. Children were mostly able to dress and wash by school age, but they needed help with fine tasks like jeans zips and buttons as well as supervision and help with washing, and especially cleaning teeth.



Support and Information

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When this leaflet was published in 2005, Unique had 40 members with a 2q37 deletion. Unique can put families who would like contact in touch with each other.

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 and has been verified by Dr Micheala Aldred, University of Leicester, 2004 and by *Unique's* chief medical adviser, Professor Maj Hulten, Professor of Medical Genetics, University of Warwick, 2005.

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