Understanding chromosome disorders

Unique

9q34 duplication syndrome

rarechromo.org

Sources

The information in this guide is drawn partly from the published medical literature. The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed/). If you wish, you can obtain most articles from Unique. In addition, this guide draws on information from a survey of members of Unique conducted in late 2011, referenced Unique.

When this guide was written, Unique had eight members with a pure 9q34 duplication (no other chromosome involved). These members ranged in age from a child of 18 months to an adult of 25 years, with an average age of 12 years. There are fifteen further people described in the medical literature, ranging in age from 1-51 years at the time of publication of the paper.

9q34 duplication syndrome

A 9q34 duplication is a very rare genetic condition in which there is a small extra piece of one of the 46 chromosomes – chromosome 9. Individuals with the 9q34 duplication syndrome have an increased risk of developmental and speech delay, learning disabilities, behavioural problems and often have a characteristic appearance of the face, hands and feet.

Genes and chromosomes

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

Chromosomes usually come in pairs: one chromosome from each parent. Of the 46 chromosomes, two are a pair of sex chromosomes: XX (a pair of X chromosomes) in females and XY (one X chromosome and one Y chromosome) in males. The remaining 44 chromosomes are grouped into 22 pairs and are numbered 1 to 22 approximately from largest to smallest. Each chromosome has a short (p) arm, (from the French for small, petit) and a long (q) arm (see diagram of chromosome 9 below).

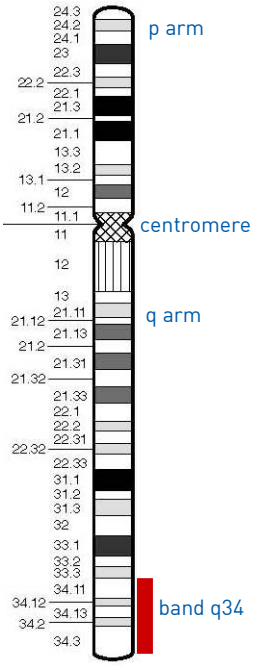
In general, the right amount of genetic material is needed for correct development – not too little or not too much. How an individual develops, his/her personality, needs and achievements, is influenced by both the genetic material he or she has and the environment in which he or she lives.

Looking at chromosome 9q34

Chromosomes can't be seen with the naked eye but if they are stained and magnified under a microscope, you can see that each one has a distinctive pattern of light and dark bands (see diagram of chromosome 9).

Each band 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. Band 9q34 has nearly 14 million base pairs. This sounds like a lot, but is actually quite small; band 9q34 is less than 0.5 per cent of the total DNA in each cell.

In the diagram of chromosome 9, the chromosome bands are numbered outwards from the point where the long arm meets the short arm.



A duplication occurs when an extra copy of a segment of a chromosome is present. In individuals with 9q34 duplication syndrome, a small amount of the end of the long arm (q) of chromosome 9 is repeated.

Genetic testing

Looking at chromosomes under a microscope, it may be possible to see the genetic material that has been duplicated, if the extra piece is large enough.

Molecular DNA technology gives a more precise understanding of the size and position of the duplication. This is important as scientists identify genes and pinpoint their location on chromosomes.

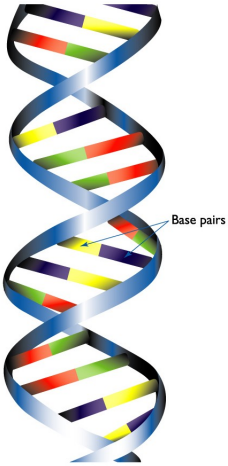
Genetic testing

Techniques that are commonly used include FISH and microarrays:

- Fluorescence *in situ* hybridisation (FISH) uses fluorescent dyes to visualise under a microscope the number of copies of small sections of chromosomes. Unique publishes a separate guide to FISH

However, rare chromosome disorders may be caused by subtle changes in the chromosomes that are too small to see using a microscope.

- Microarray comparative genomic hybridisation (array CGH) is a sensitive technique which shows gains (and losses) of tiny amounts of DNA throughout the chromosomes. Array CGH identifies duplicated, disrupted or absent DNA. Unique publishes a separate guide to array CGH.



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

A person's chromosomal make up is called his/her karyotype. Modern genetic testing can reveal the precise nature of the duplicated genetic material. Children with 9q34 duplication syndrome might have a karyotype that looks like this:

46,XX,dup(9)(q34)dn

46	The number of chromosomes in your child's cells
XX	The two sex chromosomes: XX for females, XY for males
dup	A duplication (extra genetic material)
(9)	The duplication is from chromosome 9
(q34)	The region of the long arm, q, of chromosome 9 that has been duplicated
dn	de novo (Latin for 'from the beginning)– a chromosome abnormality that has not been inherited but has arisen 'anew'.

A FISH genetic report may read as follows:

46, XX, ish dup (9)(q34.1)

46	The number of chromosomes in your child's cells
XX	The two sex chromosomes: XX for females, XY for males
ish	Fluorescence in situ hybridisation, where chromosome bands are visualised under a microscope.
dup	A duplication (extra genetic material)
(9)	The duplication is from chromosome 9
(q34.1)	The region of the long arm, q34.1, of chromosome 9 that has been duplicated

A microarray report will tell you the precise size of the duplication:

arr cgh 9q34.11;q34.13(133,354,127-134,514,500)x3

arr cgh	The analysis was by array (arr) comparative genomic hybridisation (cgh)
9q34.11;q34.13	The long arm (q) segment from 34.11 to 34.13 has been duplicated
(133,354,127-134,514,500)	An extra piece of DNA, between the base pairs 133,354,127 and 134,514,500 (around 133.4 and 134.5 Mega base (Mb) respectively from the top of the long arm where it starts counting from 0 Mb), has been found. By deducting the first number from the second, you get 1,160,373. This is the number of base pairs that are duplicated (approximately 1.2Mb)
x3	Three copies of this segment of band 9q34.1, not two – one on each chromosome 9 – as you would normally expect
Hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted

9q34 duplication syndrome

When a particular set of developmental features occurs in a recognisable and consistent pattern in enough people, as a result of a single cause, the condition is called a syndrome. The features of 9q34 duplication do occur in this way, so the disorder is known as 9q34 duplication syndrome.

The syndrome was first fully described in 1983 in a family where seven individuals inherited a chromosome rearrangement that resulted in a duplication of 9q34 (Allderdice 1983). Not all cases of 9q34 duplication syndrome are inherited.

Main features

- Characteristic appearance of the face, hands and feet – thin asymmetric head, small mouth and eyes, long thin hands and feet (that may be bent)
- Delayed development – occupational therapy can help with impaired motor skills
- Communication difficulties – speech and occupational therapy are beneficial
- Learning disabilities – learning support is often necessary
- Behavioural problems – hyperactivity and/or autism are common

These features are discussed in more detail below. The number of children with any particular feature is given as, for example, three out of fifteen published cases (3/15) or in Unique members as, for example, four out of eight members (4/8).

Pregnancy

Most pregnancies were uncomplicated and carried to term with birth by vaginal delivery at 40-42 weeks.

Two mothers had light vaginal bleeding in early pregnancy. One mother had bleeding at 22 weeks due to placenta previa; bleeding is a common symptom of placenta previa, where the placenta lies low in the uterus or womb and partially or completely covers the cervix. This mother delivered prematurely by Caesarean section at 34 weeks due to fetal distress (Spinner 1993). Another mother delivered at 36 weeks gestation; the remaining thirteen babies were born at term. Seven of the eight Unique members do not report any problems in pregnancy and had normal deliveries at term. One had a little bleeding at week 9; birth was at 36 weeks and 6 days.

There are no records of any prenatal diagnosis for either published cases or Unique members.

Newborn

Many of the newborns showed physical signs at birth.

Apgar scores are a system of evaluating a newborn's physical condition by monitoring heart rate, breathing, muscle tone, response to stimuli, and skin colour. Apgar measurements are made at one and five minutes after birth; ten is the ideal maximum score. Apgar scores were sometimes low (5/15 cases) in the first few minutes of life, for example 3-6 at one minute, rising to 6-9 at five minutes (Allderdice 1983; Spinner 1993; Duba 1998).

Lethargy was reported in several cases and hypotonia (floppiness/low muscle tone) was present in 6/15 cases in the medical literature (Allderdice 1983; Spinner 1993; Gawlik-Kuklinska 2007; Mizuno 2011) and 3/8 Unique members. Six babies were described as being cyanotic (blue in colour) and breathing difficulties were reported in four of these (Allderdice 1983; Spinner 1993; Gawlik-Kuklinska 2007). Sucking was difficult and delayed in 8/23 babies (Allderdice 1983; Spinner 1993; Gawlik-Kuklinska 2007; Unique). Birth weights are often below average with 10/15 of the published birth weights in the range 1.9-2.9kg (4lb 3oz to 6lb 10oz) (Allderdice 1983; Spinner 1993; Duba 1998; Ruiter 2007; Gijsbers 2008; Mizuno 2011). Three of the eight Unique members had birth weights in this range.

Facial characteristics (described in more detail below) can be evident at birth: narrow asymmetric faces, with prominent foreheads and small eyes and mouths.

Several Unique members reporting noticing early on that something was different about their baby. For example:

"..in the first two months her head was on one side, she had hypotonia (floppy limbs) and needed physio. She had feeding difficulties."

Feeding and growth

Feeding and growth is often affected in children with duplication 9q34 syndrome.

In the published literature, feeding difficulties at birth were noted in one child and

another had difficulty swallowing until he was 5 years old; his mouth muscles were flaccid and it was noted at 8 years that his tongue was short and deviated to the right hand side. Among the eight Unique members, five have discussed feeding problems in the early months, some of which are ongoing in older children. The slow development of fine motor skills may have a part to play in some feeding problems. Similarly, a child who had one jaw bigger than the other had a problem with biting (Unique).

One mother was able to breastfeed for 6 weeks but the baby tired quickly; weight gain was slow as a newborn. As a baby, another child had feeding problems and was allergic to baby milk, so other milks, including soya milk were introduced.
One child eats a wide variety of foods at 5 years old but still has difficulty chewing. At aged 10, another child eats small volumes of most food; along with a reduced intake of food, there was touch sensitivity to finger foods and a need for regular dietician consultations.

"She had a job to suck the teat of the bottle. She kept putting her tongue over the teat" - newborn"

"A very high palate (roof to the mouth) affected feeding as a baby."

"Some food intolerances and oesophagitis (inflammation of the tube to the stomach) have made eating difficult"- 16 years

Growth and height measurements are often plotted on a chart to show the normal range; the average is on the 50th centile (percentile), with larger measurements going up to the 99.6th centile and smaller measurements going down to the 0.4th centile. Several children had impaired growth in the early years, with weights and heights below the 10th centile for four toddlers (2-3 years old) (Allderdice 1983; Ruiter 2007). One of these children was of average height (50th centile) by 9 years old but his weight was still below average (3rd centile) (detailed records were not given for the other three) (Allderdice 1983). He had chronic constipation at 2½ years old.

Conversely, one child exhibited food seeking behaviour at 3 years old which led to obesity in the teenage years This 17 year old girl was also above average for height (170cm, 75th centile) (Gawlik-Kuklinska 2007). One 19 year old boy was on the 80th centile for weight (80.5kg) and the 40th centile for height (176cm) (Youngs 2009).

Detailed records are generally not available for older children with regard to weight and height.

Impaired growth, and weight gain in particular, was reported by four Unique members with two toddlers (18 month and 3 years old) measuring less than the 10th centile for height and less than the 1st centile for weight. One child grew very slowly and is short at 16 years old (140cm).

Three Unique members do not report height or weight issues or are described as being of average build. Conversely, at 12 years old, one Unique child was above the 91st centile for height and above the 98th centile for weight.

"She is underweight with low body fat" - 6 years

"Although weight gain was difficult in the early months, she is now 5'7" and about the right weight" - 25 years

Appearance

Facial

Children with 9q34 syndrome often have a characteristic facial appearance.

In the fifteen cases that are published, there are several facial features that are associated with the syndrome. These include an asymmetric face/skull, a long narrow head with a prominent forehead and a small mouth and eyes. Not every child will have these features, and those described and other features, like an increased width between the eyes or a receding chin, may not be very noticeable (Allderdice 1983; Spinner 1993; Duba 1998; Gawlik-Kuklinska 2007; Ruiter 2007; Guijsbers 2008; Youngs 2009; Cheung 2011; Mizuno 2011).

Asymmetric faces included a nose that deviated to one side (3/15), one side of the skull protruding more than the other (2/15) or one ear positioned higher than the other (2/15). Many of these features were evident from birth, but were also described in older individuals, including a 17 year old (Gawlik-Kuklinska 2007) and a 19 year old (Youngs 2009).

Not all children will look different from other children or other family members. Among the eight Unique members, several of the families do not report any facial differences. In others, the following features are mentioned: asymmetric face/skull (4/8), a prominent forehead (1/8), a long narrow head (3/8), small mouth (2/8) and a small lower jaw (1/8). Some of the facial features described may have medical or developmental implications. For example, several children have had teeth removed because of their small mouth (see Teeth section page 15). And in one Unique member, a small lower jaw, relative to a normal size upper jaw, led to biting difficulties in the early years.

Hands

Individuals with 9q34 syndrome commonly have unusually long, thin fingers and toes (arachnodactyly). These are likely to influence the development of motor skills (see Development: fine motor skills section page 10).

Thirteen, of the fifteen published cases, reported long, thin fingers; some were noticed as newborns, others as toddlers.

Joint contractures (inflexible joints due to shortened muscles) are present in five out of fifteen cases. Joints can become permanently flexed (camptodactyly) (4/15) and one individual had fused 3rd and 4th fingers (syndactyly) (Youngs 2009). A permanent bending of one or more fingers was present in five out of fifteen cases (two of these had clinodactyly where it is only the 5th or little finger that curves inwards) (Allderdice 1983; Spinner 1993; Duba 1998; Galwlik-Kuklinska 2007; Gijsbers 2008; Youngs 2009).

Four of the eight Unique members have long, thin fingers. Another has hyper lax finger joints, where the soft tissues holding the joint in place are very supple and the joints become very flexible. One Unique member was born with six digits on each hand (bilateral hexadactyly). This was operated on at three months.

In several cases in the medical literature and amongst Unique members, the fingers are described as becoming more crooked as the children get older.

Feet

Like the hands and fingers of individuals with 9q34 syndrome, the feet can be long with thin, tapering toes (6/15); these may overlap (2/15). Joint contractures are also reported (2/15). This is where there is a shortening of the muscle, so that there is a limited range of motion and joints cannot fully straighten. Toes may be flexed or bent. Particularly long

first toes, with a broad end, are described in 2/15 cases.

Flat feet (pes planus) are also associated with 9q34 syndrome (4/15). In addition, one child had club feet (bilateral calcaneo valgus) and by five years old had pronounced flat feet. A high arch was reported in one case.

Increased space between the 1st and 2nd toes (2/15) has been described (2/15), with fused skin of the 2nd and 3rd toes and the remaining toes flexed in one 19 year old (Youngs 2009). Three Unique members have flat feet. One of these children has a tendency to roll her feet inwards and wears insoles to help control this. Very fine toes are only mentioned by one Unique member. Another has had surgery to put misaligned foot bones back into place.

Bones/joints/limbs

Hypotonia (floppiness/low muscle tone), present in nine out of 23 cases as newborns, did not persist into later childhood in some children (Allderdice 1983; Duba 1998; Ruiter 2007; Unique). One 19 year old had hypotonia of his upper extremities and a limited range of motion of his lower extremities (Youngs 2009). Two Unique members have hyperlax (very flexible) joints.

Hypotonia is likely to make children less co-ordinated and therefore potentially prone to injury. One Unique member, who had severe hypotonia at birth, was born with a broken femur and hip dysplasia (misaligned hip joints); the hip dysplasia was treated with a Pavlik harness. Her hypotonia was subsequently moderate although she did have a broken foot at aged 2 and a broken thumb at aged 3. One boy had a congenital dislocation of the right hip and his left hip was dislocated during birth. Two children had adduction contractures of one or both hips, where the hips had decreased mobility due to structural changes in soft tissues (muscles, tendons and ligaments). One of these children also had poor movement of the right arm, whilst a fourth child's right arm was held in a flexed position (Allderdice 1983).

One boy had a repair of a dislocated knee cap (patella) when he was 11 years old; the injury was attributed to joint laxity and injuries that resulted from this (Youngs 2009). Four children had torticollis - a type of movement disorder in which the muscles controlling the neck cause sustained twisting or frequent jerking (Allderdice 1983). Three children had long, thin limbs, one in particular as a newborn (Allderdice 1983, Gawlik-Kuklinska 2007). One Unique toddler was described as having long, lean limbs; his walking was aided by a walker. Physiotherapy and occupational therapy are often reported as beneficial in children with 9q34 duplication syndrome who have hypotonia or joint contractures.

Two children had a prominent chest on one side and a third had an elongated narrow chest (Allderdice 1983). Bow legs/knock knees (genu varum) were found in two children (Allderdice 1983; Gawlik-Kuklinska 2007).

Spine

A curved spine (scoliosis) was observed in two cases in the medical literature, one of whom was 17 years old (Allderdice 1983, Gawlinka Kawlinski 2007). In another two cases, there was a fusion of two of the neck (cervical) vertebrae (Allderdice 1983). In a fifth case, a sacral dimple (a small depression in the skin at the base of the spine) was observed (Gijbers 2008).

Three of the eight Unique members have curved spines. In one child, this was improving and was hardly noticeable at 20 months.

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

Children with 9q34 duplication syndrome are often delayed in learning to sit and walk. This is often reported as one of the reasons children are referred for genetic testing. Babies who don't have a chromosome disorder generally sit unaided at around 7 months and walk on average at 13 months (age range 9-18 months).

In the medical literature on 9q34 duplication syndrome, babies were sitting unaided on average at 14 months (9q34 syndrome range 11-20 months). Similarly, Unique members were sitting on average at 12 months (9q34 syndrome range 9-18 months) and crawling at 15 months (9q34 syndrome range 11-16 months).

Walking is also delayed, with children walking on average at 2 years old (9q34 duplication syndrome range 18 months – 2½ years). An unusual or peculiar gait is sometimes described, which may relate to the flat feet and/or long, curved toes that some children have. In 8/15 published cases, walking is reported as unsteady, stiff, slow or with a broad -based gait persisting into adulthood. Two children walk with their knees flexed and their body bent forward. Short steps may be taken with frequent falls; children may run but are not as active as others of a similar age. One was cycling by 17 years of age (Allderdice 1983; Spinner 1993; Gawlik-Kuklinska 2007; Gijsbers 2008).

Amongst the eight Unique members, walking was also achieved at around 2 years old; the average was 22 months (age range 18 months - 2½ years). As in the published literature, individuals may have an unusual walk, with two children leaning forward from the waist as they walk and four walking in an unsteady fashion. One child was described as throwing one foot out when she's walking. Another wears splints on both feet since he started to walk. Physiotherapy, occupational therapy and encouraging physical activities such as tag, dancing and swimming appear to be beneficial.

"She walks with toes turned inward. Her head leads her body and she slaps her feet down loudly when she's walking" - 6 years

"She still has a strange gait and is unsteady on her feet. Swimming is a favourite physical activity, which helps her mobility" - 25 years

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

Long fingers may affect fine motor skills in children with 9q34 syndrome. Clenched and inflexible hands can make handling objects difficult. One Unique member describes how her daughter's lack of grasping skills limits her whilst another has trouble holding cutlery. Poor or slow development of fine motor skills was found in at least half of Unique members.

Development may be delayed but children are reported as using utensils, drinking from a cup and feeding themselves (Unique).

Writing can be difficult. A right-handed 8-year-old had fingers that tended to collapse, making it difficult to put pressure on a pen as he was writing. Some children are reported to have good computer skills and find using a keyboard an easier way to express themselves than writing. Coordination between the right and left hands was absent in one 2 year old (Allderdice 1983, Unique).

"Long, fine fingers makes it difficult for her to hold things" - 25 years

Unique members describe varying levels of self care.

"Now she can bath and dress herself" - 6 years

"She can dress and wash herself but need help sometimes. She can't tie shoe laces and finds buttons and zips difficult" - 12 years

"She needs help with everything; as parents we need to be very patient" - 15 years

"She's quite independent with dressing and washing herself" - 25 years

Toilet training

Children with 9q34 syndrome may be delayed in toilet training.

By 6 years old, one child was partially toilet trained in the day. The same child was dry in the day by nine years old but not always at night (Allderdice 1983).

Unique members were dry in the daytime by on average 6½ years (age range 3½-13 years). Night-time toilet training may take longer, with two Unique members reporting dry nights by 10 or 12 years old.

"Occupational therapy was useful for teaching how to wipe" - 12 years

"Accidents still happen quite often" - 15 years

Speech and communication

Slow speech development, often with long-term speech and communication problems, is a key feature of duplication 9q34 syndrome.

Twelve of the fifteen published cases were older than 2 years and 10/12 demonstrated moderate to severe lack of speech at all stages of development. For example, an 8 year old boy said only 4-5 words, a 16 year old girl had limited speech and a 19 year old boy used an augmented communication device with gestures to aid his limited aural communication (Allderdice 1983: Gijsbers 2008; Youngs 2009). Communication through gestures, signs and pictures is reported in several cases. The oldest documented case communicated with signs at 51 years of age, with a few words and no sentences (Allderdice 1983).

Other examples of children who have mastered speech are:

11-22 months –able to say 2 words such as 'Mom' and 'Dad'
3 years –beginning to form sentences
8 years – talking but speech is difficult to understand (Allderdice 1983)

All 8 of the Unique members reported significant or severe speech problems. The first sign of this was sometimes a lack of babbling or cooing as a baby. Speech therapy and sign language is regularly used to aid communication.

"She says many single words but no sentences that we understand. She talks in her own language and never stops. We see the speech therapist once a month and she has speech and language therapy at school. She uses signs (NZ sign language) well" - 5 years

"At aged 6 her communication is now mostly verbal, but at times is unintelligible."

"She communicates verbally with some gestures. She uses 2/3 word phrases, missing some words" - 12 years

"She had significant speech problems when she was younger but her speech has improved and the problems are now mild" - 14 years

"She has a few signs, often with gestures, pushing/pulling and vocal noises. She has no speech" - 16 years

"The high roof of her mouth makes T sounds difficult to say" - 25 years

Receptive language (the ability to comprehend vocabulary, directions, concepts and questions) is affected in some individuals with 9q34 syndrome. In the medical literature, one child has a severe delay in receptive language at 8 years. Others are reported as good at understanding simple directions and commands at aged 18 months - 17 years, although active speech may be absent (Allderdice 1983; Spinner 1993; Gawlik-Kuklinska 2007; Mizuno 2011).

Receptive language skills are mentioned by two Unique members:

"She is still not talking, although she says the odd word and makes lots of noises, nods for 'yes' and shakes her head for 'no'. She leads me to what she wants, understands everything and can follow instructions" - 3 years

"She has poor expressive language but uses sign language and has about 150 signs. Her receptive language is age appropriate" - 3 years

Learning

Learning disabilities are prevalent in 9q34 syndrome.

In the medical literature 13/15 children had a learning (intellectual) disability. Children can be slow to develop, a 21-month-old is functioning at a 7-9 month-old level or an 8 year old is functioning as a 4 year old (Allderdice 1983; Duba 1998). Two children were described as having a low IQ, with values in the region of 50-60 (Intelligence quotient, or IQ, is an assessment of your ability to think and reason. A score of 100 means that, compared to people in your age group, you have an average intelligence) (Allderdice 1983; Youngs 2009).

All of the 7 Unique members (those older than 2) are described as having a learning disability, ranging from moderate to severe.

At 3 years old, a child has some learning disabilities but has high concentration; she can play 1:1 for 30 minutes or so. She has special education services 1:1 four hours a week and goes to a mainstream/special needs playgroup.

One 12 year old was cited as struggling in class; getting her thoughts down on paper was difficult. Short term memory was a problem. Another child (6 years) was reported as having an average memory. Despite having a learning disability, one 12 year old was learning things much faster than expected.

In the children with more moderate learning disabilities, these had learnt to read or write around 5/6 years old. Difficulty holding writing utensils was sometimes an issue, although this was reported in one case to have improved with age.

Those with more severe learning disabilities had not learnt to read or write by the age of 13-15 years and were 10-12 years behind in their learning development.

"She is at the low end of normal for her year group" - 6 years

"She has general learning disabilities, especially sums, but her reading is good. She learnt to read and write at 5 years old but her concentration is poor" 25 years

Schooling

The published medical literature does not detail schooling of the 15 cases, except one 17 year old with moderate learning disabilities who attended a special needs school (Gawlik-Kuklinska 2007).

Of the six Unique members, where education is detailed: one is home schooled; three are in a mainstream school with, in one case, support from a speech and language unit; one is in a special education preschool. One Unique member did ASDAN in secondary school: a set of programmes and qualifications to develop key skills and life skills.

Behaviour

Children with 9q34 duplications can have a happy, affectionate and sociable nature but they also may have behavioural problems.

In the medical literature, temper tantrums, head banging and/or aggressive behaviour were described in 5/15 cases. Three individuals were hyperactive (Allderdice 1983, Gijsbers 2008, Youngs 2009). Frustration was reported due to delays in motor co-ordination and/or inability to communicate (3/15). One 19 year old boy had attention deficit disorder (ADD) and atypical autism (Youngs 2009).

Six of the eight Unique members exhibit or have exhibited challenging behaviour. Five members have had or continue to have temper tantrums, including into the late teens. Two members have ADD and one is autistic; applied behaviour analysis was being utilised. Applied behaviour analysis (ABA) makes use of scientific studies of behaviour to teach appropriate social behaviour through a system of rewards and consequences. Children with conditions such as autism find it difficult to learn from their surroundings. They have the potential to learn, but it takes a very structured environment, one where conditions are optimized for acquiring skills. ABA set ups the environment to enable learning.

Self-awareness was sometimes developing: at 7 years old, one child was beginning to notice that they were different to their peers.

Although some children may have quite severe behavioural difficulties, children may behave like their peers in their likes and interests.

"She likes playing with dolls, watching films, tag and hide and seek"- 6 years

"She enjoys computers and her DS, listening to music, cycling and pets" - 12 years

"She's severely autistic and finds social interactions difficult. Ritual playing is one of her favourite activities" - 15 years

"She's a very happy person, very sociable and willing to please"- 25 years

Medical concerns

General health and wellbeing

Children with 9q34 syndrome commonly have good general health.

Two children did have chronic middle ear infections (otitis media) (Allderdice 1983; Young 2009). One of these children also had recurrent sinusitis and at 20 months was regularly nebulised to ease congestions (Spinner 1993). The other child was prone to severe seborrhoea and pneumonia in the first few months of life. She was also blue (cyanotic) first thing in the morning, before waking; no cause was found for this (Allderdice 1983).

A Unique child had glue ear in both ears. Tiny ear canals made insertion of grommets

difficult but this was achieved in one ear; mild/moderate hearing loss has been observed. One published case had hearing loss at 16 years old (Gijsbers 2008).
Temporary absence of breathing whilst asleep (sleep apnoea) was described in one 16 year old, possibly due to deviation of the nasal septum and an enlarged tongue (Gawlink-Kaklinska 2007). This girl also had constant dribbling; one Unique member reported this although it had ceased by the time she was 25 years old.

Eyesight

A squint (strabismus) was found in approximately half of the published cases of 9q34 syndrome (7/15) (Allderdice 1983; Gijsbers 2008; Youngs 2009; Mizurro 2011). Two of these were corrected by surgery, one at 2 and the other at 6 years old (Youngs 2009; Mizurro 2011).

No squints were reported by Unique members. Three children wear glasses, one to correct short sight, the other two for long sight. One of the latter has been wearing glasses from 9 months old.

Seizures

Three children with 9q34 (two of which were toddlers) had febrile convulsions or seizures (Allderdice 1983; Cheung 2011). No Unique members are reported to have fits.

Genitals

Five children with 9q34 had genital anomalies. In particular, there were two cases of undescended testes and one case of a downward bent penis (chordee) (Alderdice 1983). One boy with underdeveloped scrotum had this corrected by surgery at 2 years old (Youngs 2009). Unique members do not report any genital anomalies.

Heart problems

Five children with 9q34 duplication syndrome had heart murmurs. A heart murmur is a particular type of noise that can be heard through a stethoscope when a doctor is examining the heart. Sometimes a heart murmur needs further investigation but often it is not serious and is not uncommon in young children. Two of these were detected at or just after birth and cleared spontaneously. Two children had a systolic murmur, which refers to the point at which the doctor can hear the murmur relative to the opening and closing of the heart valves. One child had a rare heart defect, called Ebstein anomaly, in which one of the valves of the heart, the tricuspid valve, is not formed properly and the heart works less efficiently than it should. This was diagnosed and surgically repaired at 2 months old (Mizurro 2011).

One Unique child has a small heart defect that is not of medical concern but does require antibiotic cover with dental work. Another child has a small hole in the heart wall, a ventricular septal defect (VSD), which is under observation but appears to be closing spontaneously.

Palate

Three children had a high-arched palate (roof of the mouth) (Allderdice 1983, Youngs 2009). One had hypertrophy (enlargement) of the soft palate and uvula (fleshy lobe hanging from the soft palate) (Gawlik-Kuklinska 2007).

Two Unique members had high, narrow palates; in one case this was thought to contribute to feeding difficulties as a baby and prolonged effects on speech.

Skin

Five of the fifteen published cases of 9q34 duplication syndrome had skin problems. Four of the seven family members described in the Allderdice publication (1983) had an unusual red flush on the skin. Their skin was smooth, shiny and bruised easily, suggesting peripheral vascular (blood vessel) disease. One other case had thin and easily bruised skin at 17 years old (Gawlik-Kuklinska 2007).

Teeth

A small jaw can mean overcrowded teeth; two published cases (Allderdice 1983; Spinner 1993) and two Unique members have had permanent teeth removed.

Puberty and fertility

In the three girls in whom puberty is discussed, it occurred at 14-15 years of age. In one of these cases, secondary amenorrhea (absence of menstrual periods) happened at 16 years; endocrinology revealed no hormone abnormalities (Gawlik-Kuklinska 2007; Unique).

Evidence suggests that the 9q34 duplication does not have any major effects on fertility. The study of 7 affected individuals covered several generations with inheritance through both the female and male line (Allderdice 1983). Similarly, a girl was born to parents with mild learning disabilities (and multiple affected maternal relatives) who were subsequently tested and found to carry the same 9q34 duplication (Cheung 2011).

What is the outlook?

Three adults are described (in the literature and Unique members – see below) but it is unclear, in many cases, how a child will develop with time.

Life-threatening health problems, for example, major heart defects, may occur more often in cases of a duplication of a chromosome 9 fragment that is longer than just the 9q34 region (Allderdice 1983). In these cases, treatment for heart conditions has improved greatly in recent years.

Larger duplications of chromosome 9q also appear to be associated with a more severe developmental delay (Allderdice 1983; Gijsbers 2008).

Adults with 9q34 duplication syndrome

There are three known cases of adults with 9q34 duplication syndrome. More cases are likely to be diagnosed in the future.

One case, a 19 year old boy, is described as an 18-year follow up (Youngs 2009) on the initial report (Spinner 1993). Clinical findings of 9q34 duplication syndrome were consistent with the earlier report. Limited speech was observed at 19 years of age. He was walking and running but not as active as others of his age. IQ scores were below normal at 55. Although he has a happy nature, he can become frustrated and strike out at others when agitated. He is hyperactive, has ADD and atypical autism.

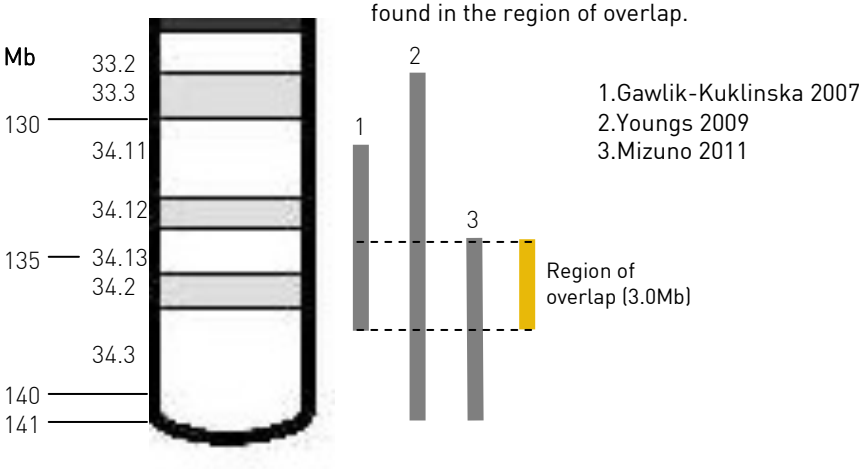
The oldest reported female died at the age of 51 from diabetes (Allderdice 1983), probably unrelated to the 9q34 duplication. Information on her characteristics is scarce.
Speech and occupational therapy, including learning a sign language, are consistently mentioned and highlighted as beneficial.

Similarly, catering for special educational needs, possibly in a residential setting can be a success in young adults. One Unique member is enjoying her placement, living in a bungalow with three others. Although she has moderate learning disabilities, she can do washing and cleaning and basic meals. She helps out in the stable and in the coffee shop once a week and likes the art and craft activities on site.

Is the size of the duplicated region of 9q34 important?

Individuals with 9q34 duplication syndrome share may similarities, hence the use of the term 'syndrome'. However, not every characteristic is present in each individual. This may be related to the size or length of the duplication. Similarly the severity of aspects of the syndrome may be influenced by the amount of genetic material that is duplicated. Chromosome 9 contains contain about 140 million DNA building blocks (140 mega base pairs - Mb) or approximately 4.5 percent of the total DNA in cells. Known cases of the 9q34 duplication can vary in length from 0.9Mb to 13.8Mb. This represents less than1 -10 percent of the total DNA on chromosome 9 and les than 0.5 percent of the total DNA in cells.

The precise length of the 9q34 duplication can vary, as shown in these three examples from the medical literature. Features common to these cases may be associated with genes found in the region of overlap.



Adapted from Mizuno 2011
Based on Human Genome build 19

The longer the length of duplication the more genes are involved. It is only recently been possible with the advent of array CGH technology to determine both the precise length of the duplicated material in any particular case and which genes are affected. The breakpoint on the chromosome where the duplication occurs may also disrupt a gene or genes.

Around 150 genes have been identified in the case of a patient with the longest duplication of 9q34 (13.8Mb) described in the literature (Youngs 2009). The products of some of these genes would be involved, for example, in the development of mental ability, soft tissue formation (and therefore limb and joint flexibility) or vital cell functions.

Potential candidates for some of the features of 9q34 duplication syndrome, among many, include: *EHMT1* (involved in the development of the central nervous system), *COL5A1* (plays a role in forming soft tissues) and *CRAT* (involved in cell function).

The features of 9q34 duplication syndrome are likely to be a result of extra copies of genes found in the duplicated region. It is important to remember that while identifying the gene(s) responsible for certain features of a 9q34 duplication syndrome is interesting and may help guide future studies, it does not lead directly to immediate improved treatment. Additionally, even if the supposedly responsible gene is duplicated 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.

Diagnosis

9q34 duplication syndrome can only be definitively diagnosed by a genetic test on a blood sample.

Children were referred for genetic testing either at birth when the physical signs were evident or when developmental delays emerged in early childhood. Two cases were late referrals in their late teens when it was not clear why there had been developmental delay (Gawlik-Kuklinska 2007; Gijsbers 2008). Unique members were diagnosed on average at 2 years old (range 2 weeks – 7 years).

"She was very slow developmentally and didn't perform well on the baby tests. She didn't walk until she was 2 and didn't talk until she was 4. She had special education needs (SEN)." (Unique)

Four published cases were initially misdiagnosed with Marfan syndrome in infancy. Marfan syndrome is an inherited condition that affects the connective tissue: the tissues that support and provide structure to other tissues and organs. People with Marfan syndrome have long narrow faces, deep set eyes, long fingers and toes, a narrow physique and long floppy limbs. However the characteristic heart and eye malformations of Marfan syndrome did not develop in these four cases and genetic testing subsequently confirmed 9q34 duplication syndrome (Allderdice 1983; Gawlik – Kuklinska 2007).

Why did this happen?

9q34 duplications can occur out of the blue for no obvious reason or they can be inherited from either the mother or the father. The only way to be certain is to check the chromosomes of both parents. If one parent has the same duplication, it has almost certainly been inherited. The syndrome was first fully described in 1983 in a family which had a history of a chromosome rearrangement involving 9q34; this resulted in seven individuals with a duplication of 9q34 (Allderdice 1983).

If both parents have normal chromosomes, the 9q34 duplication is a new occurrence. The genetic term for this is *de novo* (dn). A new 9q34 duplication has been caused by a mistake that occurred either when the parents' sperm or egg cells were formed or in the very earliest days after fertilisation. As a parent there is nothing you could have done to change or control this.

In other words, there is nothing that either parent did before or during the pregnancy that caused the microduplication.

Five of the Unique members have a *de novo* duplication of 9q34, one is inherited and two do not report this detail. Whether the duplication is inherited or *de novo,* as a parent, there is nothing you did to cause the 9q34 duplication. No environmental, dietary or lifestyle factors have been associated with these chromosome changes.

Can it happen again?

In families where both parents have been tested and have normal chromosomes, the possibility of having another children with a 9q34 duplication is almost certainly no higher than anyone else's.

Very rarely, both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 9q34 duplication. Geneticists call this germline mosaicism and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the duplication.

If either parent has a chromosome rearrangement or duplication involving 9q34 by a blood test, the possibility is greatly increased of having other affected pregnancies. In each pregnancy, someone with the duplication is likely to have a 50 percent risk of passing it on and a 50 percent chance of having normal chromosomes 9. The parent's ability to look after a child is very likely to be related to their own degree of learning difficulty.

Parents should have the opportunity to meet a genetic counsellor to discuss their specific recurrence risks and options for prenatal and pre-implantation genetic diagnosis (PGD). This procedure uses in vitro fertilisation (IVF) techniques, involves checking the chromosomes of 3-day-old embryos and only transferring those with normal or balanced chromosomes to the womb. 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 these tests are available worldwide.

"We feel very blessed with her, although life is not always easy"

Notes

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
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