

UNIQUE

UNDERSTANDING GENES & CHROMOSOMES

1q21.1 microduplications

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with a 1q21.1 microduplication. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this condition.

A 1q21.1 microduplication is a very rare genetic condition in which a tiny extra piece of one of the chromosomes is found in the cells of the body. The tiny extra bit increases the risk of learning and development difficulties. But there is wide individual variation. People with a 1q21.1 microduplication range from people with no symptoms to others with developmental delay and health problems.

Genes and Chromosomes

Our bodies are made up of billions of cells. Most of the cells contain a set of around 20,000 genes. Genes act like instructions, directing our growth and development and how our bodies work. Genes are carried on structures called chromosomes. There are usually 46 chromosomes, 23 inherited from our mother and 23 inherited from our father, so we have two sets of 23 chromosomes in 'pairs'. Apart from two sex chromosomes (two Xs for a girl and an X and a Y for a boy) the chromosomes are numbered 1 to 22. Chromosome 1 is the largest chromosome. Each chromosome has a short arm (on the left in the diagram on page 3) called p from petit, the French word for small, and a long arm called q (on the right).

Looking at chromosome 1q

Chromosomes can't be seen with the naked eye, but if they are stained and magnified under a microscope, each one has a distinctive pattern of light and dark bands. In the diagram on page 3 you can see the chromosome bands are numbered outwards from the point where the long arm meets the short arm. In a 1q21.1 microduplication, the chromosome has broken in two places in band q21.1, and a tiny amount of chromosome material between them is repeated.

Looking at chromosomes under a microscope, one can sometimes see where the chromosome has broken. With an extra piece (a duplication) that is large enough, one can sometimes see the pattern of bands that help to show how big it is.

But with a microduplication, the extra piece is so tiny that you can't see it under even the highest-powered microscope. Only molecular, DNA technology can identify it. The most common technique is known as microarrays (array CGH). This shows gains and losses of tiny amounts of DNA throughout the chromosomes. Microarrays can show whether particular genes or bits of genes are present once, twice three times or not at all.

Unique publishes separate guides to arrayCGH and SNParrays

Usual genetic variation?

1q21.1 microduplications are found in the general population as well as in people referred for chromosome testing. At first, they were thought to be part of the usual genetic variation between individuals. However, they are more common in people referred for genetic testing and they are thought now to raise susceptibility to a range of developmental disorders.

1q21.1 microduplication: two sizes

There are broadly two sizes of 1q21.1 microduplication. **Size one** spans around a million base pairs. A million sounds a lot but is actually tiny – so tiny you couldn't see it under a microscope. You would need a piece of about five million base pairs to be seen under a microscope. Base pairs are the chemicals in DNA that form 1q21.1 includes 5.4 million base pairs.

The 1q21.1 duplication is typically located between around 146 Mb and 147.8Mb in the diagram below. We know that this section includes at least nine known genes and there may be more. The numbers show a position on chromosome 1 between position 1Mb (the tip of the short arm) and position 249.25 Mb (the tip of the long arm) in the diagram at the bottom of this page (Brunetti-Pierri 2008; Mefford 2008).

bp = one base pair
kb = 1,000 base pairs
Mb = a million base pairs

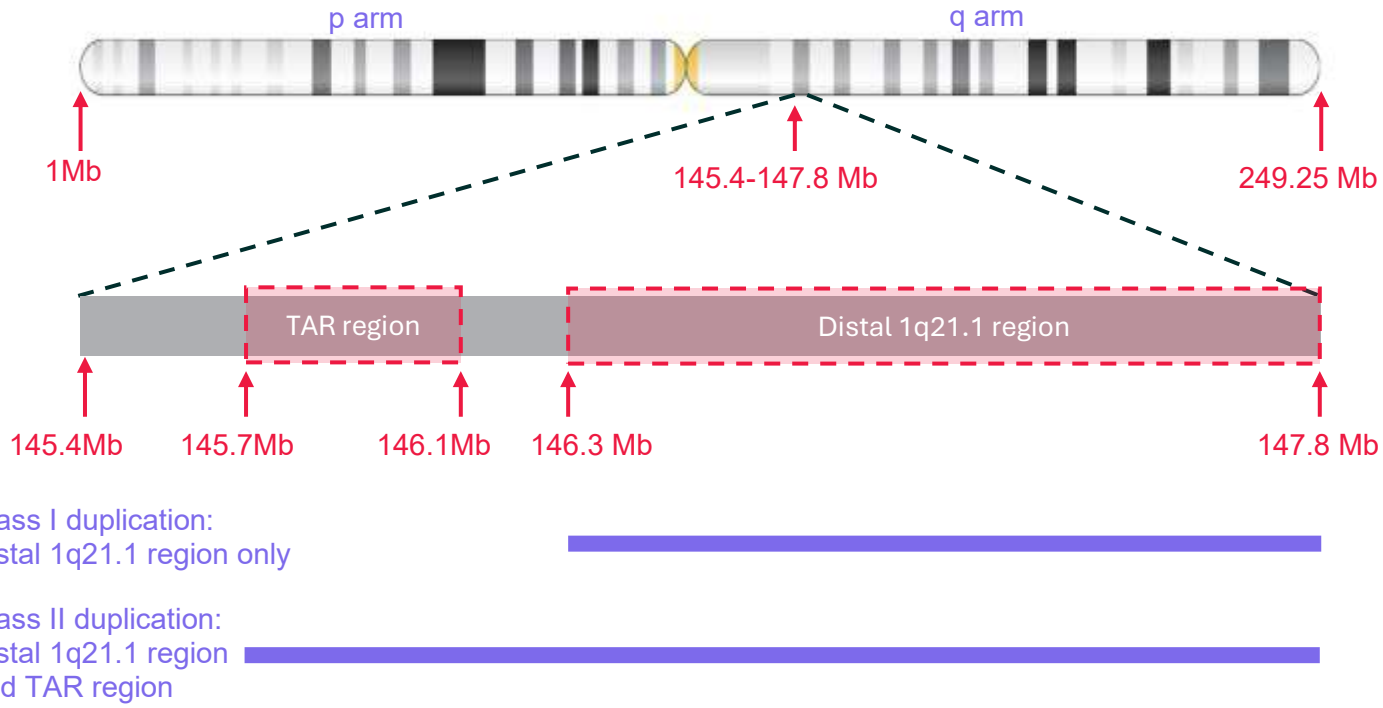


Diagram adapted from Nature Genetics Vol 40 (12) p1469 by kind permission of Dr Ankita Patel and subsequently updated. The numbers in this diagram refer to the human genome build 19 (hg19; see page 4 for more details). Your child's report may refer to a different human genome build. Please contact Unique or your genetic specialist for any help with understanding the report.

Size two is a larger duplication of around 1.35 to 2 Mb. This includes 25 known genes. This duplication is from around 145.4 and147.8Mb in the diagram below (Brunetti-Pierri 2008; Mefford 2008).

Chromosome 1



Array CGH report

The laboratory that finds the 1q21.1 microduplication will send a report that usually looks like one of these:

arr[hg19] 1q21.1(146701190-147623589)x3

arr	The analysis used microarray technology
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, "builds" of the genome are made and the base pair numbers may be adjusted
(146701190-147623589)x3	The base pairs between 146,701,190 (around 146.7mb) and 147623589 (around 147.6mb) have been shown to be repeated. Take the first long number from the second you get 922399. This is the number of base pairs, not two – one on each chromosome 1 – as you would usually expect.

Arr (RP11-337C18,RP11-533N11-102F23)x3

arr	The analysis used microarray technology
(RP11-337C18, RP11-533N14, RP11-102F23) x3	Three different markers whose position in the 1q21.1 band is known have been shown to be repeated

Occasionally you will receive a report like this. This report is not so detailed and doesn't tell you how big the extra piece is.

46,XYdup(1)(q21.1q21.1)

46	The number of chromosomes in your child's cells
XY	The two sex chromosomes: XY for males; XY for males; XX for females
dup	A duplication, or there is extra material
(1)	The duplication is from chromosome 1
(q21.1q21.1)	The chromosome has two breakpoints, both in band 1q21.1. The material between these two breakpoints is repeated.

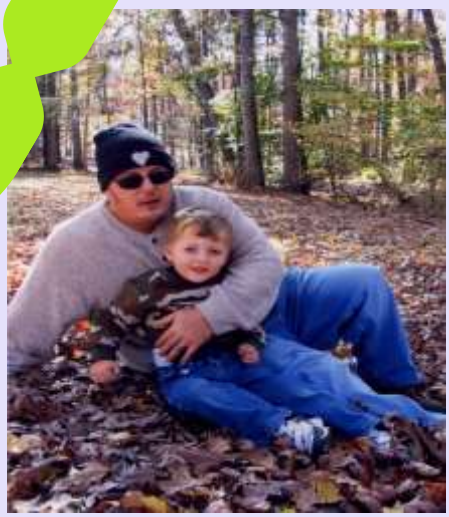
Are there people with a 1q21.1 microdeletion who have developed typically and have no health, learning or behaviour difficulties?

Yes, there are. The 1q21.1 microduplication can be silent. Some parents of children with a 1q21.1 microduplication have the same microduplication but do not have any obvious unusual features or delayed development. The signs in other parents with the duplication are so subtle that you would hardly notice. Some children with a 1q21.1 microduplication also develop typically.

The effect of some genetic variants like this ranges from being barely perceptible to being obvious and severe. In this sense they are like infections such as flu that can be mild or more serious (Brunetti-Pierri 2008; Mefford 2008; Aldinger 2009; Stanciewicz 2010).

Is there a 1q21.1 microduplication syndrome?

No, there isn't. The features associated with a 1q21.1 microduplication are too varied to be called a syndrome.



A common situation: both father and son have a 1q21.1 microduplication. But the father's microduplication was only found after it was found in his son

Most likely features

- Relatively large head
- Increased possibility of mild or moderate developmental delay
- Increased possibility of autism or autistic-like behaviour
- Slightly unusual facial features
- Heart problem

Other features

- Seizures
- Increased risk of other inborn anomalies

Most likely features

Relatively large head



Studies have shown that around a half or more people with this microduplication have a large head or a head that is large compared with their body. This suggests that the microduplication influences brain growth. Quite a lot of people with a missing copy of this section of chromosome 1 (a microdeletion) have an unusually small head and this also supports the idea that a gene or genes within the deleted or duplicated section influence head growth. Researchers have identified a gene (see Some genes in 1q21.1, page 19) that is likely to be important in determining head growth.

Although a possible link has been suggested between a small head and mental health problems, particularly schizophrenia, no such link has been suggested for people with a large head (Brunetti-Pierri 2008; Mefford 2008; Aldinger 2009).

Among Unique members with this microduplication, head size is variable. Four out of nine members have a large or relatively large head. Two Unique members were born with the bones of the skull already fused (craniosynostosis). After successful surgery and re-shaping, head growth was average in both cases. Neither child has had seizures.

"I ride a motorbike and I always need the biggest helmet." – Adult with 1q21.1 microduplication

Brain

Among 27 cases reported in the medical literature, three have a structural brain anomaly. In one case the band of nerve fibres linking the two sides of the brain was thin (hypoplastic corpus callosum) and the narrow worm-shaped structure between both sides of the cerebellum, an area at the back and bottom of the brain that plays an important role in movement and co-ordination (cerebellar vermis), was also underdeveloped. One person had a protrusion of the cerebellum part of the brain into the spinal canal (Chiari malformation). One had a build-up of fluid within the brain (hydrocephalus) (Brunetti-Pierri 2008; Mefford 2008). No Unique members reported anomalies of brain structure (Unique).

Increased risk of developmental delay and learning difficulties

Some children with a 1q21.1 microduplication develop at a usual rate, cope well academically and grow up into adults who take their place in society as expected. Others are slow to reach their developmental milestones, need extra help at school and may need special schooling. This means that a baby or child with the microduplication should be monitored vigilantly for delay and extra help and therapies should be offered promptly.

Having the microduplication does not make it possible to predict how mild or pronounced any delay and learning difficulties might be. The spectrum includes people who have no noticeable problems – and some who are severely affected. Researchers have found that the delay is typically mild or moderate (Mefford 2008; Aldinger 2009; Unique).

Among Unique members, the range of developmental delay is broad, from none to severe. Babies and toddlers may be late to reach their developmental milestones (sitting, crawling, walking) and fine motor control, toilet training and personal care skills (dressing and undressing, self-feeding, washing) may also be delayed. Among adults apparently unaffected by the microduplication, there may be subtle signs.

> ***Excellent fine motor skills." – age 3***

"Very sloppy writer. Limited dexterity for small items." - Adult with 1q21.1

Increased risk of autism or autistic-like behaviour

Children and adults with a 1q21.1 microduplication can be affectionate and sociable with no behaviour problems. But a minority of them may be at risk for a range of behaviour difficulties and autistic-like behaviours. However, we do not know yet whether these unusual behaviours are a result of the 1q21.1 microduplication or a chance association. In one series in the medical literature, four out of eight children had a diagnosis of autism and one had challenging behaviour; in another series of 24, two had autism or autistic features; one had attention deficit hyperactivity disorder and one had a mood disorder (Brunetti-Pierri 2008; Mefford 2008; Aldinger 2009).

Among Unique members, three out of 11 have a diagnosis of autism or an autistic spectrum disorder. Other features remarked upon by families include: difficulty relating to other children, perhaps because of their unpredictable behaviour, and clear preference for adults (four children, three age 3 and one almost six); whining and tiring easily and moodiness associated with epilepsy (age 3). The child who was almost six also showed somewhat rigid thinking and behaviour as well as inappropriate friendliness and anxiety. Two children are reported to need a lot of sensory stimulation. One adult reports having had counselling for 'anger problems'.

> ***She is loving and likes to be held and hugged; beautiful smile and sweet and gentle." – age 2***

"On a usual day he is pleasant and happy, smiling and laughing. Due to a sensory processing disorder he wears under arm compression shirts on the advice of his occupational therapist and a compression vest during the day at school. These calm him down so he is not constantly seeking some sensory input." – Age 3

"He is an enormous people pleaser. It is very important for him to make other people happy even at his young age. He is really very sweet and can switch easily to a very cuddly, kissy mood. He wants cuddles all the time and wants to stroke my hair and I have to stroke his hair." – Age 3

Slightly unusual facial features





Most children and adults with a 1q21.1 microduplication look like other members of their family. Doctors trained to observe unusual features may notice things such as widely spaced eyes or a prominent forehead, but these signs can be subtle and not obvious. In around half the cases reported in the medical literature, at least slightly unusual facial features were noted. Unique parents have also commented in their children on a wide Like the rest of the glabella (the space between the eyebrows and above the nose) family: 1];
prominent eyes, lessening with age [1]; a small nose [1]; prominent epicanthic folds (folds of skin across the inner corner of the eye) [1]; a wide, flat nasal bridge [1]; and low set ears [1] (Brunetti-Pierri 2008; Mefford 2008; Aldinger 2009; Unique).

A photo gallery of adults and children with the microduplication has been published (Brunetti-Pierri 2008) and is available to families from Unique on request.

"Beautiful features; no very obvious differences." – Age 2

Heart problem

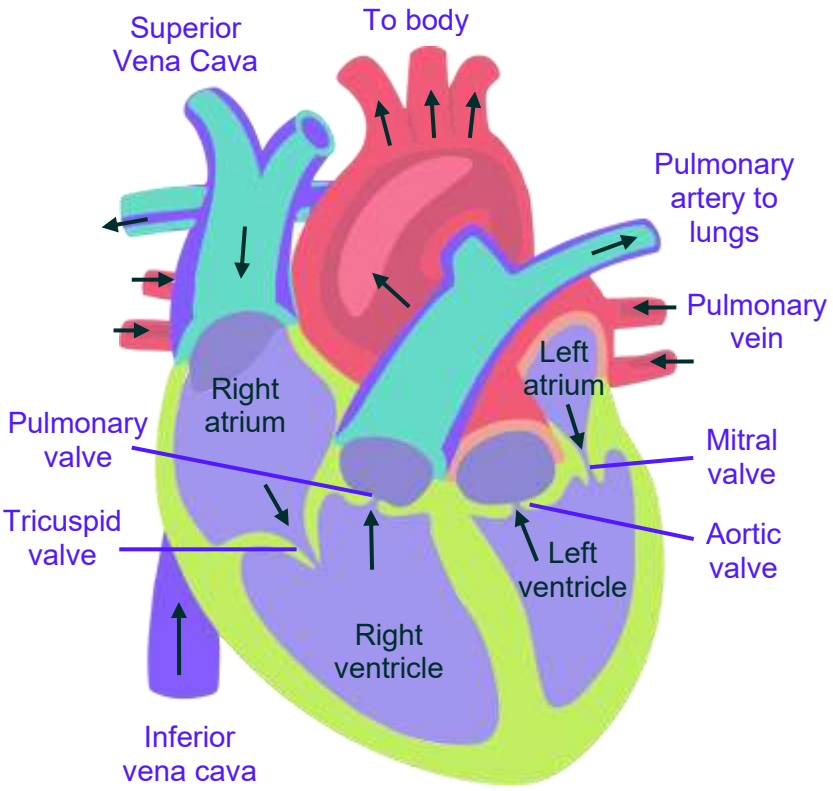
It is uncertain whether having a 1q21.1 microduplication puts a baby at risk of being born with a heart problem. Some researchers have found more babies born with structural heart problems than would be expected, but others have not. Overall, four out of 35 babies were reported in different series in the medical literature. Of these, two had a ventricular septal defect (VSD, see page 9); and in one there was a univentricular heart (see page 9) (Brunetti-Pierri 2008; Mefford 2008). Another person was reported with a microduplication of the TAR region (see page 3) inherited from his father (Brunet 2009). He had complex heart problems including transposition of the great vessels, a VSD, pulmonary stenosis and an underdeveloped right ventricle (see below and page 9). Among Unique members, 7/31 were born with a heart problem, including 3 with a VSD, one with pulmonary stenosis, one with stenosis of the pulmonary veins, one with an unspecified hole in the heart that is closing naturally, and one with unspecified chronic heart failure. Two babies were born with tetralogy of Fallot [ToF]. Five of the 7 needed surgery to correct their heart problem (Unique).

One study of ToF found that almost 1 in 100 babies had either a microduplication (4/512) or a microdeletion (1/512) at 1q21.1 – a much higher rate than would be expected by chance. These babies had a heart defect but no cognitive, social or neurological problems (Greenway 2009). Of the two Unique children with ToF, one has a moderate-to-severe degree of developmental delay, while the other was too young to assess (Unique). Two genes have been identified that may contribute to heart problems (see Some genes in 1q21.1, page 19). The heart problems diagnosed in individual children may be single or multiple. They include:

Ventricular septal defects (VSDs) - holes in the wall between the two pumping chambers of the heart (ventricles). This allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Treatment is determined individually. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from extra blood flow.

Transposition of the great vessels - the main blood vessels (aorta and pulmonary artery) leading from the heart are reversed. A baby with this condition usually needs surgery very soon after birth.

Pulmonary stenosis - The entrance to the artery that takes blood to the lungs is unusually narrow. The narrowing usually affects the pulmonary valve and the pulmonary artery itself.



Pulmonary vein stenosis - There is an obstruction (blockage) in the blood vessels that bring oxygen-rich blood from the lungs back to the heart. It can occur in just one pulmonary vein but most often is found in multiple veins simultaneously. The obstruction is due to a thickening of the walls of the veins. Surgery to widen them is usually a short-term solution.

Tetralogy of Fallot - A complex heart condition involving both a VSD and an obstruction just below the valve in the artery that leads to the lungs. Blue (deoxygenated) blood cannot easily get to the lungs to pick up oxygen and some of it flows through the hole into the other pumping chamber from where it is pumped around the body. If there are no other risk factors, more than 95 per cent of babies with tetralogy of Fallot successfully undergo surgery in the first year of life.

Univentricular heart - Univentricular means that there is a single ventricle [lower, pumping chamber of the heart] instead of two ventricles but in reality this is rare. More commonly, the term 'univentricular heart' describes a heart where blood from two upper chambers [atria] flows into a dominant right or left lower chamber [ventricle] via a defective connection. Another way to describe this is as a double inlet ventricle. Typically, there is a non-dominant, underdeveloped second ventricle. A univentricular heart usually needs surgical repair.

"Fine now after heart surgery." – Age 3

Other features

Seizures

Seizures have been reported in five/35 people in the medical literature and in four/11 Unique members. Among the Unique members, 'absences' or seizures started in early to mid-childhood. They are reported to be controlled with standard anti-epileptic medications such as sodium valproate (Brunetti-Pierri 2008; Mefford 2008; Unique).

Spinal curvature

One case of spinal curvature (scoliosis) in a series of 24 was reported in the medical literature (Brunetti-Pierri 2008). Within Unique, there are four out of ten reports, two involving otherwise healthy adults. A two-year-old baby developed a curvature by six months which measured 30 degrees by two years; she was treated with a back brace. A teenager developed a severe scoliosis after a growth spurt. Two adults reported minor problems.

> ***When I signed up for the army the doctor told me I have a little curve in my spine but that was no objection to my doing military service. Nothing serious" – adult***

Minor genital anomalies

Minor genital anomalies have been reported in three out of 27 cases in the medical literature, such as hypospadias (the hole is on the underside of the penis instead of being at the tip) or testicles undescended at birth. Both of these anomalies can be corrected, if necessary, with surgery (Brunetti-Pierri 2008; Mefford 2008). Among nine Unique cases, one baby boy was born with undescended testicles and another with ambiguous genitalia. In both cases surgery was needed (Unique).

Increased risk for other inborn anomalies

Other minor or more serious birth defects have been seen, but these don't appear to follow any pattern and it is uncertain whether there is any causative link or not with the 1q21.1 microduplication. The reports in the medical literature include: a small sacral dimple at the base of the spine [1]; a hemivertebra (incomplete development of one side of the vertebra, resulting in a wedge shape) [1]; loose or dislocatable joints [2]; multiple joint contractures at birth, known as arthrogryposis [1]; clubfeet [1] (Brunetti-Pierri 2008; Mefford 2008).

At birth

Most Unique families report an straightforward pregnancy, with one report out of nine noting lack of fetal movement. Babies were generally born at or near term and were a good size at birth, ranging from 2.69 kilos (5lb 15oz) for a baby induced for pre-eclampsia at 35 weeks to 4.36 kilos (9lb 10oz) for a baby at full term. Most babies were healthy, although the baby born at 35 weeks had jaundice. One baby was extremely colicky and another – despite a good birth weight and Apgar scores (a measure of wellbeing at birth) – looked and behaved like a premature baby, with a red skin, sleeping a lot, needing waking for feeds and struggling to maintain his temperature.



Feeding

Among nine Unique members, five had no feeding difficulties and breastfed successfully. One baby breastfed but remained underweight. One baby born with craniosynostosis was tube fed for two weeks but was bottle feeding by the third week. The baby who behaved like a premature baby was too weak and lacked necessary reflexes to suck.

He was woken every two hours to be given expressed breast milk from a feeding cup. After two weeks, the gaps between feeds at night were lengthened. Seven weeks later he was strong enough to start breastfeeding and continued for two years. He was delayed in drinking from any other source but learned to drink from a cup at two. Despite this tricky start, he eventually responded enthusiastically to solids.

One child ate well but had difficulty handling cutlery, preferring to use his hands, and needed weighted cutlery. One child remains a very fussy eater at six years and refuses any food with lumps, such as a fruit yoghurt.

Two Unique members report gastro-oesophageal reflux, where feeds return into the gullet and can be vomited or may be inhaled, causing chest infections known as aspiration pneumonia. In one instance this affected an adult; the other case involves a six-year-old child who brings up stomach fluids when she leans forward.

> ***He is a good eater. When he was about eight months, we started to introduce real meals and he was really enthusiastic. He ate anything and a lot! There were times when we just had to say no because he ate the same amount as his grandma. At the moment he eats usual amounts and its going well." – Almost age 3***

Growth

Out of 27 cases reported in the medical literature, growth was typical in 22. Three babies or children experienced failure to thrive, where the growth rate is unusually slow; in one there was uneven growth and one child had an advanced bone age (Brunetti-Pierri 2008; Mefford 2008). Among nine Unique members, growth was average in four, two were short and one of them was slim. Two children are tall and one is thin. Four families comment that their child is stocky or above average weight.

> ***Thick build; when others pick him up, they comment on how stocky he is." – Age 3***

"If I had to describe him as tall, short or average it would be short but he is actually more squat. He has a big head and his arms are a bit too short. The rest of his body is typical. A year or two ago he looked a bit fat and chubby but he is now well proportioned." – Age 3

Health and wellbeing



Infections are common in childhood. There is no evidence that children with 1q21.1 microduplications are more prone to infection than other children, although one family reports that their three-year-old son catches every cold doing the rounds and had many respiratory problems as a baby and young child. Another family reports that their child had numerous infections including pneumonia and meningitis before the age of two. This family and one other report that their child's health deteriorates rapidly when they are ill. Two children have asthma or asthma-like symptoms, and one has a mitochondrial Complex IV condition for which he takes coenzyme Q10. Four people have been reported with a skin condition: one with psoriasis and three with eczema. It is known whether these conditions are related to the 1q21.1 microduplication or not. Between illnesses, parents report that their children are healthy, happy and making progress (Brunetti-pierri 2008: Unique).

"I think it also effects his respiratory problems. He can't cough as strongly as other children so phlegm stays in his lungs." – Age 2



Hearing

Ear infections are common among young children, including those with a 1q21.1 microduplication. They are reported in one out of 24 people in the medical literature (Brunetti-Pierri 2008) and two out of nine Unique members, both of whom had tubes (grommets) inserted to equalize pressure on either side of the ear drum. Neither child had a permanent hearing loss but one had sensory problems and was hypersensitive to loud noises and frightened of harsh sounds (Unique).

"When he was born and, in the months, afterwards, he never looked straight at us. He couldn't follow us around with his eyes. At 10 weeks, we went to an eye doctor, but he couldn't find a cause. It took over five months before he looked right at us for the first time."



Sleep

Five out of ten Unique members report some degree of difficulty with sleep. One baby was very hard to get to sleep for the first four months; one child is very restless and moves continually while asleep at age six; one is hard to put to sleep and wakes at night but stays asleep with a sound machine; one is awake every night from 2-3 until about 6 o'clock; and one is both hard to settle and requires very little sleep. It's not clear yet whether children with a 1q21.1 microduplication have greater sleep difficulties than other children or whether there is a pattern of sleep disturbance linked with the microduplication (Unique).

Learning

In those people with a 1q21.1 microduplication who do need extra support with their learning due to learning difficulties, the degree of difficulty has been described in eight out of 11 as at least mild or moderate (Mefford 2008). Unique's experience reflects this, with a very wide range of abilities among its membership. One adult with the microduplication runs his own business; another has a masters degree. Among the children, any effects on learning are highly variable. The comments below illustrate this rich variety.



"She has a good memory and learns best with a consistent approach. She looks at books but can't read yet and scribbles if a pen is put in her hand." – age 2

"We don't think he has a learning difficulty or disability. He has a very good ear for music and enjoys singing a lot. He can do puzzles of 50 pieces on his own! He doesn't like anything that would make his hands dirty like play-doh or paint. He is obsessed by toy cars and real cars and knows some makes and points them out. He gets very excited when he plays with his toy cars and he sees the wheels spinning. His memory is typical and he enjoys learning new things. He doesn't like to draw but if he does, he scratches with his pencil. He is too young for a computer but I don't expect problems. He will attend a special school for children with communication and/or autism problems." – Age 3

"He has an excellent memory: he can remember words to songs but at times won't say his name. If passing a restaurant, he will say the food he wants or ate there eg hotdog, chicken. Music is a more able area. He is lazy, to be honest: if he has no interest in what he is learning, he will not participate. He is always 'reading' books. He looks at the pictures and babbles about the book. He hates drawing and colouring. He is highly interested in computers but not the keyboard. He will put his hand on top of an adult's on the mouse and click the button. He attends special education pre kindergarten, with learning support from a special education teacher." – Age 3

"She can count to 10 but not read. She can write her first name. She likes to use the computer at school. She attends mainstream school in a speech/ language programme but does not have a statement of special educational need." – Age 5½



Communication

In the medical literature there are three reports out of 24 of delayed speech skills in children with a 1q21.1 microduplication (Brunetti-Pierri 2008). Among Unique members, delayed speech and language is a consistent finding even among adults who otherwise have only very subtle signs that can possibly be ascribed to the microduplication. Frequent themes are better understanding than ability to express in speech and lack of clarity with the sounds of speech. One child successfully communicated his needs initially with sign language, moving on to speech in mid childhood and fluent speech by adolescence. Children are sometimes educated in speech and language units, focusing on communication skills.

"She communicates with vocal noises." – Age 5 months

"She communicates with signing, gestures, pointing, pulling and sounds but has difficulty with all speech sounds." – Age 2 years 5 months

"He tries to speak but he can't always make clear what he means. There are problems between what his brain thinks and what his mouth can say. According to tests that his speech therapist did he understands a lot more than he can say or make clear to us. So we use a lot of yes/no questions. For the past six months we have been using hand signals and pictograms. We see that it makes him sad and sometimes angry if we just don't understand what he wants to say. His speaking voice is very soft and unclear and if you ask him to say something again, he shuts down completely. He spoke his first word around his first birthday and is now using 2/3 word phrases but a lot of words sound the same when he says them." – Age 3

"He communicates by showing with his hands: he takes your hand and touches the object he wants. He started to use words at 2½, using one word to say what he wanted. He now uses 1–3-word phrases but most sounds are not clear. He talks a lot, just no one can understand him." – Age 3

"Strangers struggle to understand her. She has good expressive language but poor receptive language." – Age 5½

"I didn't have speech therapy but I started talking a bit late. For a long time I pointed out at everything I wanted." – Adult with 1q21.1 microduplication



Nine months old



27 months old



Three years old

Mobility

It is too early to know whether there is any consistent effect of this microduplication on mobility skills but at present this does not seem to be the case. In families where a parent had been found to have the microduplication after a child was diagnosed, mobility in the parent is usually unaffected, even if the child has delayed mobility.

Children with a 1q21.1 microduplication who do have developmental delay may need extra help in reaching their 'baby' milestones such as sitting and moving around. Children with a low muscle tone (hypotonia) will benefit from physiotherapy and all children benefit from regular graded exercise to build up their strength and agility. Among Unique members with developmental delay, babies learned to roll over between five and 10 months. They sat between six and 16 months; became mobile (shuffling, creeping or crawling) between seven and 20 months; and learned to walk between 13 and over 60 months. Children mastered climbing stairs between 18 months and three years.

"When he sat up at first he couldn't sit straight, he sat a bit like a pudding. Crawling he did very late because he has limited rotation of his torso. When he was one year old (around his birthday) he started to slide, bumping and bouncing on his bottom. He did that until he could walk at about 23 months. Now he is nearly a typical child of almost 3 years. He still has limited rotation of his torso so turning around takes a bit more time. He has some balance problems. The physiotherapist thinks that because his body proportions are slightly atypical - he has a big head and short arms - he falls a lot. His arms are hypermobile so it is difficult for him to break his fall and he often lands flat on his face. He has a special buggy if we want to walk long distances and the buggy is made so it helps him sit up straight and he has a helmet to make his falls a bit less painful." – Age 2

"He has some sensory processing difficulties, so is always moving and jumping. He loves to climb and swing." – Age 3

"She moves fast; trips and falls a lot; is anxious using stairs." – Almost age 6

Why are people with a 1q21.1 microduplication so different from each other?

We don't understand this properly yet. Consistent differences haven't yet been detected between people with different-sized microduplications - and people in the same family with the same size microduplication can have very different features.

One reason for the uncertainty is that the 1q21.1 band of chromosome 1 has such a complex structure that its precise DNA sequence has not been completely mapped. There are still 15 gaps in the map and it's possible that genes exist in these gaps that contribute to the effects of the microduplication. In addition, there are probably other genetic and environmental factors that we don't yet understand but are important.

Why are people tested for the 1q21.1 microduplication?

Most babies and adults are tested because the paediatrician or specialist doctor looking after them suspects there may be a chromosome problem. The 1q21.1 microduplication sometimes explains the presenting problems; in other cases, it's thought to be irrelevant. Until more people have been diagnosed with this microduplication, the full range of its effects will not be known.

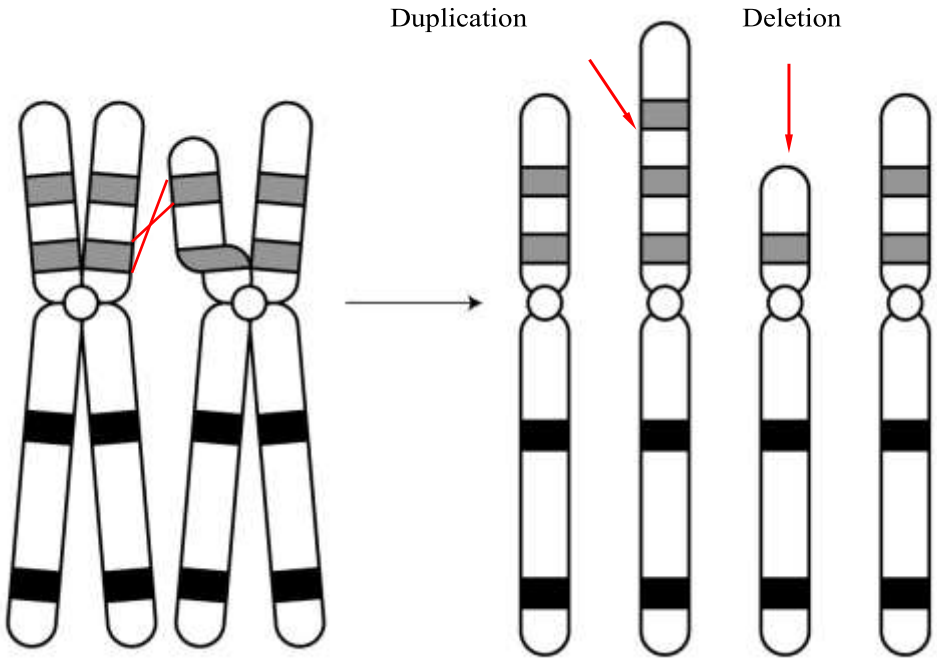


Among Unique members, two babies were investigated because of craniosynostosis (early fusion of some of the bony plates that form the skull). In one case, later development was unaffected and the craniosynostosis was not ascribed to the microduplication; her father carries the same 1q21.1 microduplication. In the other case, the contribution of the 1q21.1 microduplication
remains uncertain. One child developed seizures at six. Four children had developmental delay, in one case associated with unusual facial features; another baby had a spinal curvature and developed seizures at 18 months; another baby was very limp at birth but had no heart problems. Four of the seven children inherited the microduplication from their father or mother who until then had no reason to suspect anything unusual about their chromosomes.

How did this happen?

1q21.1 microduplications 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. The parents' chromosomes should be checked even if they are themselves completely healthy with no developmental problems at all.

If one parent has the same microduplication, it has almost certainly been inherited. If both parents have usual chromosomes, the 1q21.1 microduplication is a new occurrence. The genetic term for this is de novo (dn). A new 1q21.1 microduplication 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.



At one point during the development of egg and sperm cells, all the chromosomes including the two chromosome 1s pair up and swap segments. To pair up precisely and ensure that the swapped segments are equal, each chromosome 'recognises' matching or near-matching DNA sequences on its partner chromosome. However, throughout the chromosomes there are many DNA sequences that are so similar that it is thought that mispairing can occur. This then causes unequal swapping, leading to either a deletion or a duplication.

The 1q21.1 region has an extremely complex structure. Three-quarters of it consists of at least four blocks of DNA that are more than 90% similar to each other. It is quite likely that these very similar blocks have caused a mispairing. When researchers examined the breakpoints in the chromosome in individual people, they found that they fell within these near-matching DNA sequences. In most people, the breakpoints occurred within parts of them that are virtually identical.

If one person in a family with the 1q21.1 microduplication is mildly affected, will other in the same family also mildly affected?

Not necessarily. There is a lot of variation between different members of the same family. We know that if one person is mildly affected, others may be more severely and obviously affected.

Can it happen again?

Where both parents have usual chromosomes, it is unlikely that another child will be born with a 1q21.1 microduplication or any other chromosome disorder. Very rarely (less than 1%), both parents have usual chromosomes by a blood test, but a few of their egg or sperm cells carry the 1q21.1 microduplication. This is called germline mosaicism and it means that parents whose chromosomes appear usual when their blood is tested can have more than one child with the duplication.

In families where the 1q21.1 microduplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 1q21.1 microduplication rises to 50% in each pregnancy. However, the effect of the microduplication on the child's development, health and behaviour cannot be reliably predicted.

Your genetics centre should be able to offer counselling before you have another pregnancy.

Will my child with a 1q21.1 microduplication have similarly affected children?



Your child with a 1q21.1 microduplication may well want to have children. We have not known about the condition for long enough to be certain if it affects fertility but it is likely that fertility will be typical. In each pregnancy, someone with the duplication has a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the duplication. Their ability to look after a child is very likely to be closely related to their own learning ability.

Some genes in 1q21.1

The part of 1q21.1 that most people have duplicated is rich in genes.
GJA5 is a gene that produces a protein known as Connexin40. It's expressed in the upper chambers (atria) of the heart and not having enough is associated with congenital heart problems. Some people who do not have this gene have usual hearts, though, and the reason for this is not fully understood (Christiansen 2004; Mefford 2008; Brunet 2009). PRKAB2 is another gene that's expressed in the heart (Brunet 2009).

The HYD1N gene found on chromosome 16q22.2 has a part copy that was inserted into 1q21.1 during evolution. The HYD1N gene on 1q21.1 is only active in the brain. In individuals in whom it is missing, head size is small, while individuals who have an extra copy of this gene have a large head. This strongly suggests that the HYD1N gene plays a role in determining head size (Brunetti-Pierri 2008; Mefford 2008).

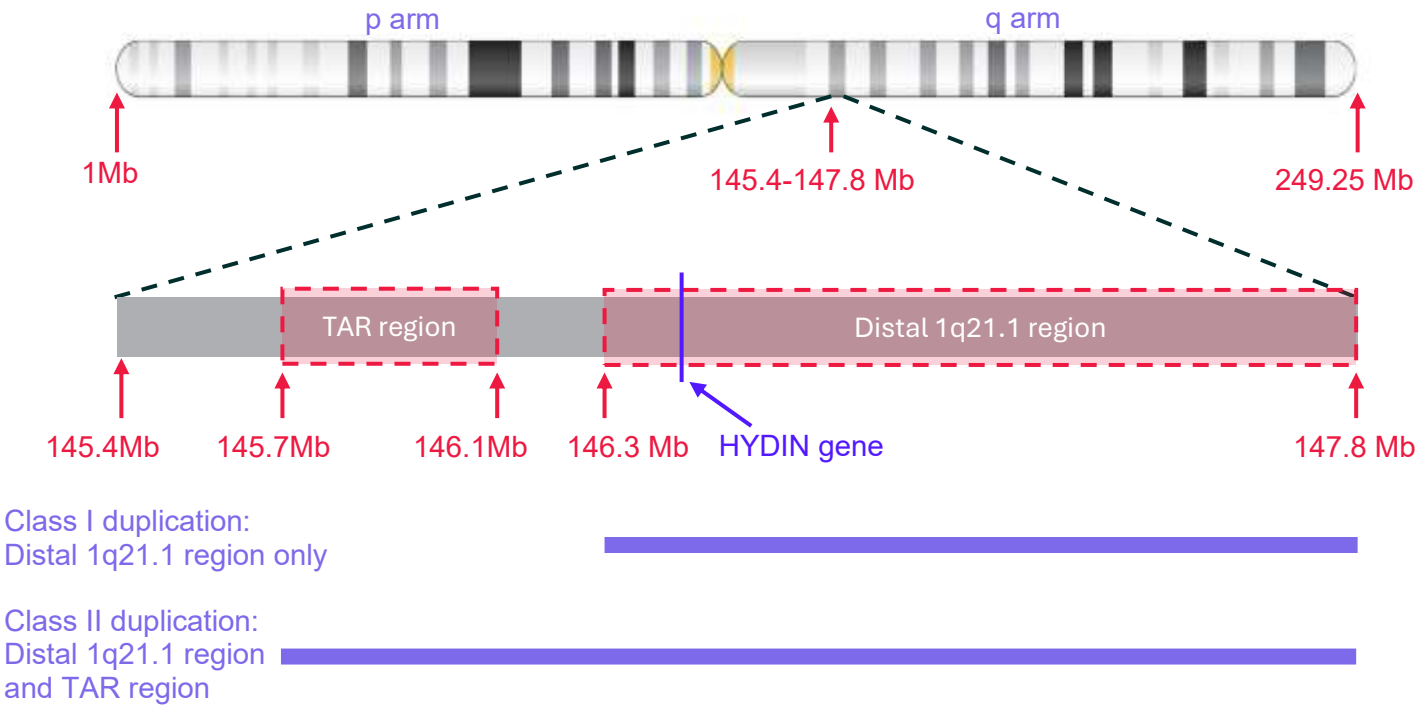


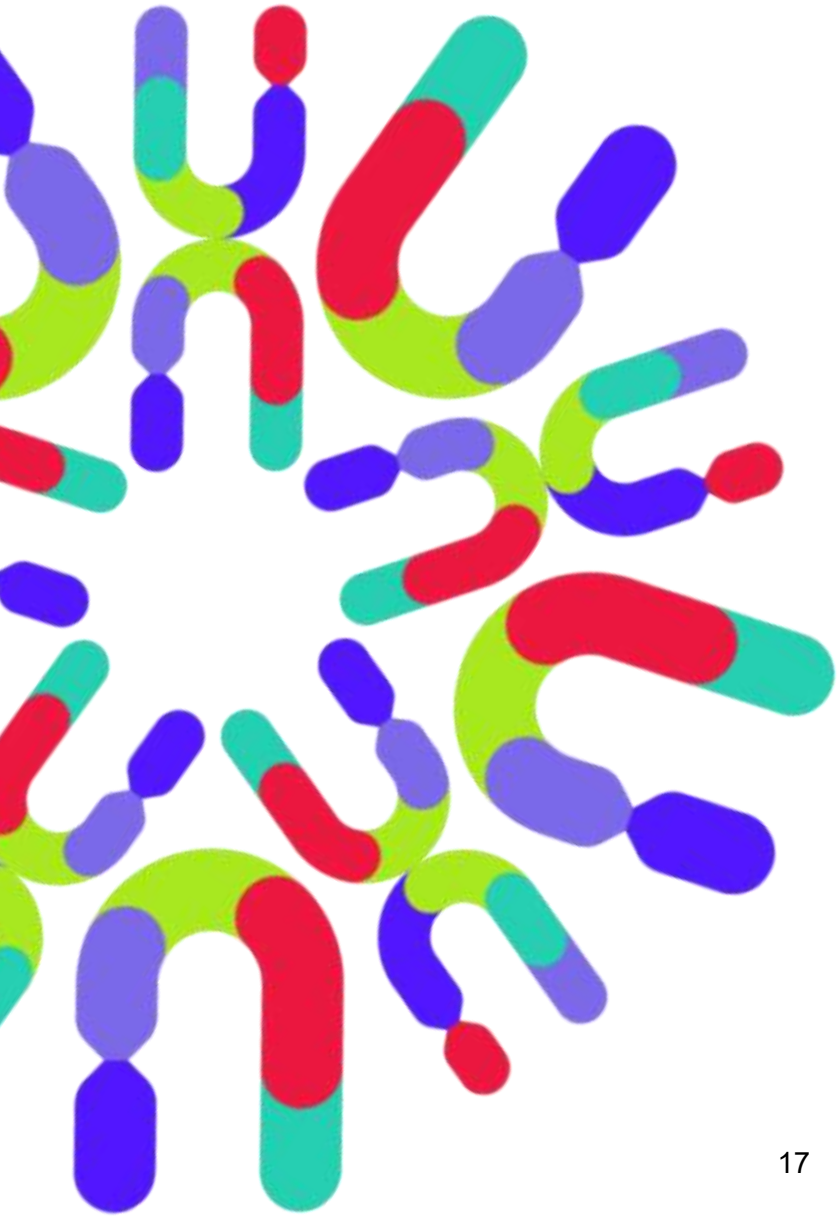
Diagram adapted from Nature Genetics Vol 40 (12) p1469 by kind permission of Dr Ankita Patel and subsequently updated. The numbers in this diagram refer to the human genome build 19 (hg19; see page 4 for more details). Your child's report may refer to a different human genome build. Please contact Unique or your genetic specialist for any help with understanding the report.

Sources and references

The information in this guide is drawn from what is known about around 50 people with a 1q21.1 micro - duplication.

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 articles from Unique.

The leaflet also draws on Unique's database (BrunettiPierri 2008; Mefford 2008; Aldinger 2009; Brunet 2009; Greenway 2009; Stanciewicz 2010; Unique).



Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey, RH8, 9EE, UK
Tel: +44(0)1883 723356
help@rarechromo.org I rarechromo.org

Join Unique for family links, information and support:

Become a member

Please help us to help you!

Unique is a charity without government funding, existing entirely on donations and grants.
If you can, please make a donation:

Donate via our website

Alternatively, donate via this QR code:

Websites, Facebook groups and other links:

- **There is a Facebook (www.facebook.com) group for families affected by 1q21.1 microduplications called 1q21.1 microdeletions and microduplications**

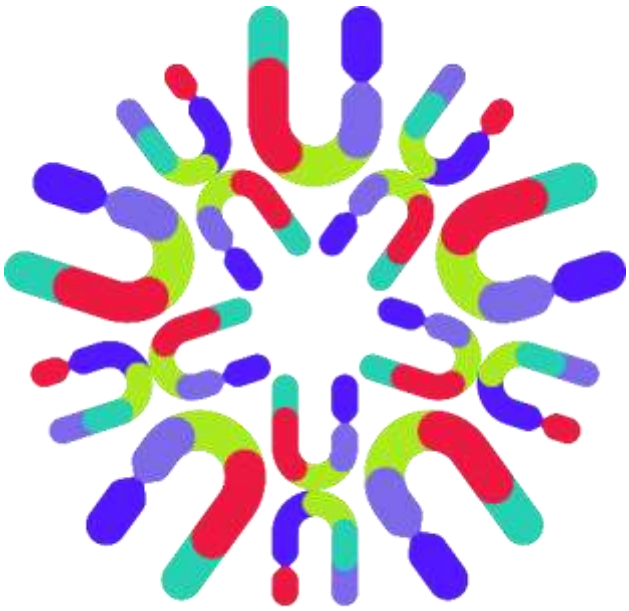
Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This guide 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 reviewed by Dr Heather Mefford, Assistant Professor, Pediatrics, Division of Genetic Medicine, University of Washington, USA and by Unique's chief medical advisor Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, 2010.

Copyright © Unique 2010

Rare Chromosome Disorder Support Group
Registered in England and Wales

Charity Number 1110661
Company Number 5460413



unique

UNDERSTANDING GENES
& CHROMOSOMES

rarechromo.org