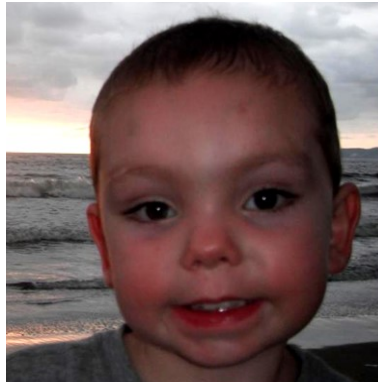




Understanding Chromosome & Gene Disorders

3q29

Duplications and Microduplications



rarechromo.org

Sources & References

The information in this guide is drawn from what is known about a small number of people - just 23 - with a 3q29 duplication.

Fifteen people have been described in varying detail in the medical literature, some with slightly smaller or larger microduplication sizes. 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). There is a literature list on page 15. You can get articles marked Free access yourself on the internet. If you wish, you can obtain other articles from *Unique*.

The guide also draws on *Unique*'s database. When this guide was written, *Unique* had eight members with a 3q29 duplication or microduplication, of whom three had a larger duplication extending as far as band 3q27 and two a duplication extending to band 3q28. One girl has a mosaic chromosome make-up: some of her cells have normal chromosomes, while others have the 3q29 duplication (Willatt 2005; Rooms 2006; Rosenberg 2006; Ballif 2008; Goobie 2008; Lisi 2008; *Unique*).

“ While knowing your child has a chromosome disorder is scary, each child is different. The 3q disorder is so unknown at this point. I searched everywhere trying to find answers to what our future might bring. While it is important to know what to look for and what might be coming, the best thing I did for myself and my family was relax. I have learned to enjoy my son for who he is and accept that we will deal with whatever may come. He has a special quality that everyone who knows him can see. Nobody has been able to put a name to it yet, but we all can see it and love it. ”

A 3q29 duplication is a rare genetic variant in which there is a tiny extra piece of one of the body's 46 chromosomes. This tiny extra piece is found in virtually all the cells in the body that are needed for growth, development and healthy functioning. Some people have the tiny extra piece of chromosome without noticing any problems. Others have developmental delay and perhaps some health difficulties. There are quite big differences between individual people who have a 3q29 duplication. Overall it seems that having the extra chromosome piece increases the risk of problems but this is not always the case.

Chromosomes are the structures inside the body's cells that carry DNA, the genetic information that tells the body how to develop and function. They come in pairs, one from each parent, and are numbered 1 to 22 approximately from largest to smallest. Each chromosome has a short (p) arm and a long (q) arm.

Looking at 3q29

Chromosome analysis

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a high-powered microscope, you can see that each one has a distinctive pattern of light and dark bands. You can see these bands in the diagram of the long arm of chromosome 3 on page 3. The bands are numbered outwards starting from the point at the top of the diagram where the short and long arms meet (the **centromere**). A low number such as q11 is close to the centromere. A high number such as q29 is very close to the end of the chromosome, at the bottom in the diagram.

If you magnify the chromosomes to hundreds of times life size and look at them down a microscope, there may be a small extra piece visible on the long arm of chromosome 3. This is called a 3q29 **duplication**.

Microarrays and other technologies

The extra piece may be so subtle and tiny that even when the chromosome is magnified many hundreds of times it looks normal down a microscope. The extra piece can then only be found using a combination of different techniques including looking at the chromosomes down a microscope, FISH [fluorescence in situ hybridisation] and, increasingly, a technique known as chromosomal microarrays or array-CGH. Such a tiny extra piece of a chromosome is called a **microduplication**. A microduplication in the 3q29 band of chromosome 3 is called a 3q29 microduplication.

There is a short length of DNA within band 3q29 that contains around 22 known genes. When people have *lost* this length of DNA they usually have features of a condition known as **3q29 microdeletion syndrome**. People who have an extra copy of this length of DNA have what we call in this guide ‘the typical 3q29 microduplication’. While some people have an extra copy of just this section, others have an extra copy of a longer or a shorter bit of the chromosome, including part or all of this section. This means that they have extra copies of different genes and it’s believed that these different genes cause some of the major differences between individual people with a 3q29 microduplication.

The genetic test results

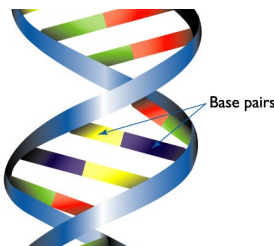
Your geneticist or genetic counsellor will give you your child’s genetic test results. If the test used chromosomal microarrays, the result is likely to look something like one of these:

arr cgh 3q29(197,415,249-198,816,466)x3

arr cgh The analysis used microarray technology (197,415,249-198,816,466)x3 The base pairs between 197,415,249 (around 197.4 Mb) and 198,816,466 (around 198.8 Mb) have been shown to be repeated. Take the first long number from the second and you get 1,401,217. This is the number of base pairs that are repeated. This can be rounded to 1.40 Mb. **x3** means there are three copies of these base pairs, not two – one on each chromosome 3 – as you would expect.

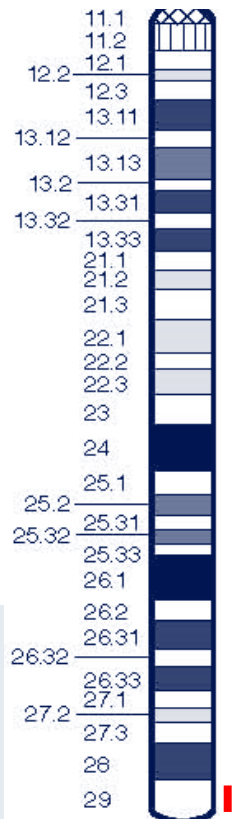
arr cgh 3q28q29(RP11-962B7->RP11-159K3)x3

arr cgh The analysis used microarray technology **3q28q29** The duplication here starts in band 3q28 and finishes in band 3q29 **(RP11-962B7->RP11-159K3)x3** The test showed extra copies of two different markers whose position in bands 3q28 and 3q29 are known.



Bases are the chemicals in DNA that are linked in pairs to form the ends of the ‘rungs’ of its ladder-like structure. One thousand base pairs is often written as 1 kb. One million base pairs is often written as 1Mb.

Chromosome 3: long [q] arm



Occasionally, you will receive a report like this. This report is not so helpful, because it doesn't tell you how big the extra piece is.

46,XX,dup(3)(q29)

46	The number of chromosomes in your child's cells
XY	The two sex chromosomes: XX for females; XY for males
dup	A duplication, or there is extra material
(3)	The duplication is from chromosome 3
(q29)	The duplication is in band 3q29

The report may show the letters **dn**. This is the short form of **de novo**, Latin for 'from the beginning'. This means that the parents' chromosomes have been checked and no change found at 3q29. The duplication is very unlikely to be inherited and has occurred for the first time in this family with this child. If the letters **pat** are given, then the duplication is inherited from the father. The letters **mat** mean that it's inherited from the mother.

Are there people with a 3q29 microduplication who have developed normally and have no health, learning or behaviour difficulties?

Yes, there are, many. The 3q29 microduplication can be 'silent'. When a child is found to have a 3q29 microduplication, the parents' chromosomes will also be tested. In many cases, a parent who is entirely normal and healthy also has the 3q29 microduplication. You may well wonder how that can be. We are not yet quite certain. One idea is a 'two-hit' hypothesis: a child with the 3q29 microduplication needs another subtle chromosome change for development to be disrupted and symptoms to show. The tens of thousands of genes on the other chromosomes must also play a role. Another point is that chromosome changes cause a range of effects from barely noticeable through mild and moderate to severe. In this sense they are like infections such as flu that can be mild or severe. So some members of a family can have barely noticeable effects, while others are more obviously affected (Rooms 2006; Rosenberg 2006; Ballif 2008; Goobie 2008; Lisi 2008).

Suggested guidelines for the management and anticipatory care of people diagnosed with a 3q29 duplication or microduplication

A team of geneticists from Europe and Canada has suggested that people diagnosed with a 3q29 duplication receive these assessments and services:

Babies and at diagnosis:

- Eye evaluation
- Electrocardiogram
- Brain imaging
- Developmental assessment by 6 months and every 1-3 years as needed
- Hearing check
- Skeletal survey
- Early intervention services
- Family support

Childhood:

- Ongoing developmental services and therapy, with an individual education plan [IEP], statement of educational need or equivalent if needed. Likely benefit from occupational therapy, speech and language therapy and physical therapy.

- Referral to paediatric dentistry
- Encourage physical activity and a balanced diet

Adolescence & adulthood:

- Annual medical examination as standard medical practice
- Ongoing developmental services, learning support and counselling about work placement
- If appropriate, education about sexual development and likelihood of the microduplication occurring in any children [Goobie 2008]

Most likely features

- Generally healthy, without major birth defects
- In some cases, a delay in overall development
- Considerable differences between individuals in terms of learning ability but some will do better at school with learning support
- Some speech delay
- Possibly, eye anomalies
- Possibly, heart anomalies
- Possible tendency to overweight

■ Generally healthy

Most individual people described in the medical literature and members of *Unique* are healthy, with few chronic diseases. One man had high blood pressure, gout and diabetes as well as kidney insufficiency, but he was significantly overweight. One child had frequent hospital admissions for infections in her first year but was healthy by the age of 8. One child had asthma, but that is common in the general population and there is no evidence that it is caused by a 3q29 microduplication [Goobie 2008; Lisi 2008; *Unique*].

“ A happy and general healthy child. He has had his share of colds that would always turn into ear or sinus infections – 3q?27q29 duplication, 3½ years

“ Very healthy. He does not get sick very often, less than most kids – 3q29 microduplication, 6½ years

■ Usually without major birth defects

The great majority of babies have been born healthy and without important birth defects. Most of the unusual features listed here have been found in only one child, raising the question whether the chromosome duplication was really the cause. A number in brackets indicates the number of cases.

Arms, legs, hands and feet. No anomalies of the arms, legs, hands or feet have been noted in the nine people with the typical 3q29 microduplication. Among 12 people with a larger duplication, three babies were born with dislocatable or dislocated hips, in two cases needing immobilisation to correct the hip joint. Easily dislocatable hips are also found fairly commonly in babies with no known chromosome disorder. The most obvious limb defect occurred in a baby with a 2Mb 3q29 microduplication who was born without legs or left arm and with his right arm extending



In a Pavlik harness to stabilise the hips

only part way below the elbow. However, it's likely that these defects were caused either by some other subtle change in his chromosomes or by an unrelated factor rather than by the 3q29 microduplication. Another child was born with the two bones in the forearm fused together [radioulnar synostosis], quite a common finding among those with a chromosome disorder. A child with a larger 3q27q29 duplication was born with one tiny extra finger [Goobie 2008; *Unique*].

High but not cleft palate [split in the roof of the mouth] (1). Only one of the nine people with the typical microduplication has an unusually high palate. Of those with a larger 3q29 duplication, two have a cleft and one has a high palate [Goobie 2008; *Unique*].

Hernia [umbilical]. This has only been found in one baby with a larger 3q29 microduplication of around 2.4Mb. The hernia was successfully repaired surgically at a second try when the baby was 20 months old. This baby also had a separation of the right and left sides of the muscle that covers the front surface of the abdomen known as diastasis recti, which was also repaired, and an abdominal cyst that was removed [Goobie 2008].

Minor anomalies of the genitals and bottom. No genital anomalies were found in people with the typical microduplication. A man with a 2 Mb microduplication – so somewhat larger than the typical one – and another with a 3q27q29 duplication were born with hypospadias, where the hole normally at the end of the penis is sited on the underside instead. In the case of the first man, the left testicle did not come down into the scrotum and was removed when he was 15 years old because it had withered. A baby girl was born with the anus placed somewhat far forward [Goobie 2008; *Unique*].

Bladder defect [patent urachus] (1, larger duplication). One baby was born with an opening between the bladder and the umbilicus. This opening nearly always closes before birth and can be surgically repaired [*Unique*].

■ In some cases, a delay in overall development

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

The scant information that exists on the development of gross motor skills among children with the typical 3q29 microduplication suggests that any delay will be minor. However, with very little information, any statement must be preliminary and may change as more information emerges. While one baby sat, crawled and walked at an appropriate age, another - who had mild low muscle tone - was somewhat delayed, sitting by 17 months, walking by 2½ years and needing physical therapy and shoe inserts to help support the arches and with balance at 6½ years [Lisi 2008; *Unique*].

“ He is a fine walker and runs on his own, though not as fluid as other 6-year-olds. He gets tired on longer walks, but with lots of encouragement has gone on light hikes. He can swim and ski by himself but while other 6-year-olds are starting to play soccer, he is not ready. We are an active family and have a pool which has been wonderful – a real source of fun and confidence building. His favourite activities are swimming, skiing, sledding, shovelling and anything involving helping outdoors and he also likes to ride his bike (with training wheels) - 6½ years

Among those with a larger 3q29 duplication, even one extending to 3q27, any delay appears to be typically minor, although there is one report of a baby with a more significant delay and 4/13 babies are reported to have low muscle tone [hypotonia]. Babies first learned to roll over between 6 and 12 months, to sit between 9 months

and 2 years, to crawl or become mobile in another way between 11 and 24 months and to walk between 14 and 30 months. There are three/13 reports of clumsiness, frequent stumbling or ataxia [unsteadiness] [Rosenberg 2006; Goobie 2008; *Unique*].

“ Once his open heart surgery had healed he caught up nicely and now walks, runs, and jumps above his age level. Although occasionally his ankle clonus [a rhythmical muscle contraction after a sudden stretch, caused by raised muscle tone] can be witnessed, it has had no effect on his movements and is normally stable - *3q27q29 duplication, 3½ years*

“ She walks well now but tires quickly and most enjoys riding and swimming. She is still unsteady at times, especially when climbing up and coming down stairs and needs her hand held. Her most useful therapies have been horse riding, hydrotherapy and trampoline – *3q29 mosaic duplication, 5½ years*

■ **Hand eye coordination, personal care (fine motor skills)**

The 10 reports of individual children’s development affecting their fine motor and personal care skills show a wide range: from young children who appear to be unaffected, through others with mild delays to a 16-year-old who is not yet toilet trained.

“ Slow, steady improvement in fine motor skills. Very little independent care but has started to put on shoes on her own, takes coat off after it has been opened - *3q29 mosaic duplication, 5½ years*

“ He has delays in fine motor skills. He can use eating utensils without a problem, but has a hard time writing letters and numbers. His eye to hand coordination is not that of his siblings. When he was younger, we used cans with small openings in them a lot. He would put pennies or other smallish objects into the cans through the small opening on the top. He liked this and the repetitive practice helped. He also loved playing with trains and trucks, which helps. Today he can dress himself for the most part but needs help with some things. Overall he does quite well with self care. It took him much longer to potty train, and he still prefers help with ‘wiping’, but otherwise he does himself. This took until he was turning 6 - *3q29 microduplication, 6½ years*

■ **Considerable differences between individuals in terms of learning ability but some will do better at school with learning support**

It seems that having the typical 3q29 microduplication raises an individual child’s risk of having learning difficulties and needing support or special education in school. While many relatives of people with 3q29 microduplications discovered through family screening are unaffected, among the nine detailed reports of affected people, seven have a mild to moderate learning difficulty.

As youngsters with a 3q29 duplication or microduplication are at risk for a learning disability or specific learning difficulties, assessment and support should be provided when any concerns are first expressed and if necessary formal assessment of educational needs should be fast-tracked.

“ He attends school with children of his age but is behind them in developmental progress. Nothing comes to him intuitively and he has to work very hard to learn everything. I would say he is roughly 12 – 30 months behind on most subjects and skills in learning. He can count. He knows most letter sounds and many of the colours.

His teachers say he continues to make steady progress. His memory seems to be good. He remembers things from the day before and months before. He is starting to show a little bit more strength in mathematics, which seems to run in the family. He will listen to books but he does not yet read. He can write his name but it is still very hard to read. He can draw some shapes but with his level of muscle control is still very hard. He has basic computer skills, but we have limited computer and video game time so he has not had a chance to really develop this yet.

He has had an IEP [individual education plan] for each year he has been in school. He does the social pieces of the day with the other kids, then he is separated to a special small classroom with one teacher and two kids for the learning portion.

To learn well, he needs lots of little physical breaks and little incentives. He is very distractible, so keeping him on task is tough. Teachers need to be willing to let him get up and walk around for a while if they then want him to focus - *3q29 microduplication, 6½ years*

Among those with a larger 3q29 duplication, there is a wider range, from age-appropriate learning at three years through a moderate level of learning difficulty at 17 years [*Unique*] to a profound learning disability [Goobie 2008]. Among those with a learning difficulty who need special support at school, very good outcomes are possible. One young man with a significant birth defect [missing legs and arm] and learning difficulties went to college and was living independently and working in customer care at the age of 30. Another was working voluntarily in his local library at 17 [Goobie 2008; *Unique*].

“ She has started to read in her native language, likes to look at books and make up her own stories. She likes drawing people and animals - *3q29 mosaic duplication, 5½ years*

■ Some speech delay

With only one report detailing speech and language abilities, it is uncertain whether the 3q29 microduplication implies a specific risk of speech delay. The affected child first smiled at an appropriate age [2 months] but was late to say his first words [30 months]. At 6½ years, he communicates effectively by speaking, can talk in short sentences and hold a short telephone conversation. His speech is less clear than other children's [specific difficulties sounding 'th' and 'l' sounds like 'w'] but he is generally well understood. As his speech has improved, the gap between expression and understanding has narrowed [*Unique*].

“ He often surprises us with the questions he asks: they can be very insightful - *6½ years*

Among those with a larger 3q29 duplication, most children appear to have a mild to moderate speech delay, although some reports suggest a more significant problem. Babies appear to communicate well, smiling responsively at an appropriate age or just slightly late. Babbling has emerged between 4½ and 23 months and first words from the second half of a baby's first year. Most children show a discrepancy between their understanding and their expression and some have difficulty controlling and coordinating the movements of their tongue.

“ He produced his first words at a year but is currently in speech therapy. His language skills are developed but he has a hard time with pronunciation and is hard to understand - *3q27q29 duplication, 3½ years*

“ She has had speech therapy and made good progress with a good level of speech now and conversing fluently - 3q29 mosaic duplication, 5½ years

A few children have had repeated ear infections, with the possibility of a temporary hearing loss caused by fluid within the ear, but there is no evidence of any permanent hearing loss. All the same, the temporary hearing loss can occur at a critical time for speech development and children with this type of [conductive] hearing loss may well have tiny plastic tubes [grommets] placed temporarily in the ear drum until the glue ear and fluctuating hearing loss resolves.

As children are at risk of speech delay, parental concerns should be acted on early and home or school-based therapy provided. Some children have successfully learned to sign and made the transition from signing to speech.

■ Possibly, eye anomalies

Among babies with the typical microduplication, no structural eye defects have been found and none have been found among *Unique* members with the typical microduplication or a larger duplication. Two babies with slightly larger than the typical microduplications of 3q29 [2.08Mb and 2.4Mb respectively] were born with eye defects: one baby had very small eyes [microphthalmia], a developmental defect of the right iris known as a coloboma and clouding of the cornea [front part] of the right eye as well as a cataract of the left eye. This baby had the cornea transplanted and the cataract was removed at four months. The second baby had a developmental defect of the left iris. A boy with a 3q27q29 duplication was born blind in one eye [Goobie 2008; *Unique*].

■ Possibly, heart anomalies

There are five reports of structural defects of the heart, including three babies born with a hole between the two upper or lower heart chambers. No two babies were born with exactly the same problems and severity has varied greatly.

Among the babies with the typical microduplication, one was born with a hole between the two pumping chambers of the heart [ventricular septal defect, VSD]. A VSD allows blood to flow from the left to the right chamber, increasing the blood flow to the lungs. Specific treatment for VSD is determined individually. Small VSDs may close spontaneously; a larger VSD usually needs surgical repair to prevent lung problems that would develop from exposure to extra blood flow. Another baby was born with the most common heart defect, a bicuspid aortic valve. This valve controls blood flow from the heart to the body via the aorta. The valve normally has three flaps [valves], but a bicuspid valve has only two. Often no treatment is needed but the abnormal valve may not completely stop blood from leaking back into the heart. The valve can also become stiff and not open up so well, making the heart pump harder to get blood past. If this occurs, surgery is possible [Ballif 2008; Lisi 2008].

Among babies with a slightly larger microduplication, one had a tiny hole between the two upper collecting chambers of the heart [atrial septal defect, ASD] but had no symptoms and needed no treatment. Another had a complex defect known as an atrioventricular septal defect which creates a large hole in the middle of the heart connecting the two upper chambers (atria), the two lower chambers (ventricles) as

well as a single valve instead of two separate valves on either side of the heart. This was surgically repaired leaving her generally healthy.



Getting better after complex heart surgery



A member of *Unique* with a duplication from around 3q27 to 3q29

was born with another complex heart condition known as Fallot's tetralogy. This involves both a hole between the lower pumping chambers of the heart 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. Children with tetralogy of Fallot will need a surgical operation and *Unique's* member is doing well 3½ years later [Goobie 2008; *Unique*].

■ Possible tendency to overweight

Four/nine people with the typical 3q29 microduplication are technically obese and one is above both average weight and height. Having said this, three of the nine are related, and other members of their family are also obese. The two other family members with the 3q29 microduplication were both young babies and were in the bottom five per cent of their age group for height and in one case for weight as well [Ballif 2008; Lisi 2008; *Unique*]. Among those with a larger 3q29 duplication, three were unusually short, a 16-year-old was obese and a 30-year-old had excess fat, with stretchmarks over the abdomen and torso. *Unique* children in this group were of average height and at 5½ years one has a weight problem which is managed without much success by encouraging physical exercise and providing a healthy diet [Goobie 2008; *Unique*].

But usually without feeding problems

Feeding difficulties are very common among babies and children with chromosome disorders but most babies and children with a 3q29 duplication do not have any difficulty with feeding. Reports from *Unique* show that successful breastfeeding is common and that even young children eat a variety of foods. A small number of families report that their child has had gastro oesophageal reflux, where feeds and stomach contents return readily up the food passage and are often vomited or may be inhaled, causing chest infections, known as aspiration pneumonia. Reflux can be managed by positioning a baby upright or semi upright for feeds and by raising the head end of the

cot for sleep. If treatment is needed, anti-reflux milks are available, as well as thickeners for other drinks. Prescribed anti-reflux medications are available and in severe, persistent cases, surgery can correct the problem. However, there are no reports of anyone with a 3q29 duplication having reflux severe enough to need surgery. Constipation is also common among children with chromosome disorders but is reported by only one *Unique* family, treated with prescribed stimulant medication.

Other issues

■ Head and brain

Among people with the typical microduplication, 7/8 have a head that is in some way unusual. Five have a very small head [microcephaly], four of them from the same family. One - the father or grandfather of the four relatives with a small head - has a very large head [macrocephaly] and in another some of the bony plates that form the skull knitted together too early [craniosynostosis].

Among people with a slightly larger 3q29 microduplication, two babies were born with a large fontanelle [soft spot] on top of the head and one had an unusual square-shaped head, short from front to back [brachycephaly]. One *Unique* child has a large head. The great majority of babies, children and adults with a 3q29 microduplication appear to have a normal brain structure when examined by magnetic resonance imaging. There are four reports of abnormalities, all in children with a duplication larger than the typical one. One child had symptoms that would fit a diagnosis of Dandy Walker variant, a mild form of Dandy Walker syndrome caused by abnormal development of part of the bottom part of the brain. Another child had a small cerebellar vermis; defects in the development of the cerebellar vermis are associated with ataxia, a neurological disorder in which the parts of the nervous system that control balance and co-ordination do not function correctly, causing unsteady movements. A third child had Arnold Chiari malformation, an abnormality of the base of the skull where parts of the brain and where the brain connects with the spinal canal, known as the brainstem, bulge into the spinal canal. If there is any evidence of raised fluid pressure within the brain, a shunt can be inserted for drainage. The band of nerve fibres that connects the two hemispheres of the brain was thickened in a fourth child [Goobie 2008; *Unique*].

■ Epilepsy

There have been no reports of seizures among people with the typical microduplication. Among *Unique*'s seven members with a somewhat larger duplication, three have seizures. One of these is a girl with a mosaic chromosome make-up and in another the duplication extends beyond 3q29. In one child seizures resolved by the age of 5 years and in another they were controlled by anti-epileptic medication. No information was available for the third child [*Unique*].

Behaviour

While a 3q29 *deletion* or *microdeletion* appears to increase vulnerability to difficulties with social relationships and communication, this does not appear to be the case for those with a 3q29 *microduplication* or *duplication*. The one child for whom detailed information is available from *Unique* is described as 'very social', 'will talk to anyone, and is 'a flirt of sorts'. He possibly has attention deficit hyperactivity disorder but has not

yet responded to medication. 'Occasional bouts of frustration' at 3½ developed into difficulties with temper control at 6½: depending on sleep, hunger and mood, small things could set him off.

“ He was a loving, calm, happy, mellow baby who slept well and never cried. At 3½, he was very affectionate, personable and happy with only occasional bouts of frustration. Today he is still very affectionate and loving and not afraid to express his feelings. He also likes to 'press buttons' which can be funny, unless it is you and you are already upset - 6½ years

Among those with a larger 3q29 duplication, one eight-year-old girl is reported to be 'very pleasant and friendly' with no behaviour problems [Goobie 2008]. *Unique* families also consistently report good social interactions with adults and children. One child displayed some autistic behaviours [such as lining up toys] but failed to meet the criteria for a diagnosis of autism, while a 17-year-old has a diagnosis of autism and significant behaviour problems. Temper tantrums are the most characteristic behaviour challenge.

“ His behaviour is normal for a 3-year-old, perhaps a little shy at times - 3q27q29 duplication, 3½ years

“ She is well behaved at school but has moods at home if she does not get her own way and has temper tantrums that we have been told to ignore; she then calms down and acts as if nothing has happened - 3q29 mosaic duplication, 5½ years

“ A very gentle, sweet baby with a very endearing personality and way with him through early childhood. As he got older, his behaviour became more challenging and difficult. Autistic traits have become more obvious over the years. By 17 he has become defiant when told what to do. Loud outbursts of verbal abuse and swearing can ensue, many offences were impulsive with much contrition later. He now takes risperidone and has regular behaviour therapy and has settled down. Throughout he has retained much of his endearing charm - 3q27q29 duplication, 17 years

Appearance

Two babies with a duplication larger than the typical one were born with an unusual amount of body hair [*Unique*]. For many babies and children there may be little sign in their facial appearance of any underlying disorder. Children with 3q29 duplication rarely look unusual or 'different' and no typical pattern of features has emerged.

Two babies were born with a 'strawberry' birth mark known as a haemangioma. Most strawberry marks resolve spontaneously in time but may need special care until they do [Goobie 2008; Lisi 2008].

“ A very handsome little boy which has worked to his advantage as many teachers and therapists adore him.

Outlook

While 3q29 duplications have been diagnosed for many years, microduplications have only been diagnosed in the last few years. This is not long enough to be certain what the long term effects are. As most people with these duplications have no birth defects and are generally healthy, however, it seems likely that they will have a normal life expectancy.

Genes

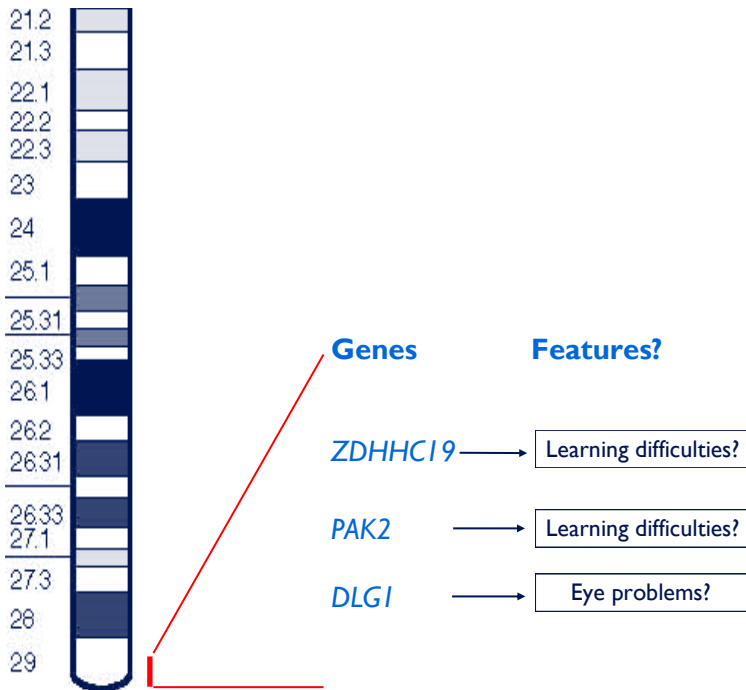
People with the typical 3q29 microduplication usually have extra copies of 20-22 genes covering a length of around 1.6Mb of the DNA in the chromosome. The function of most of these genes is not yet known, but having this extra copy of some of these genes has been suggested as the possible cause for certain symptoms [Goobie 2008; Lisi 2008].

DLG1 may cause eye anomalies. *DLG1* provides some of the instructions for making a protein that is important in creating parts of the eye and more generally the head and face [Goobie 2008; Lisi 2008]. 196769431-197026171

PAK2 is related to *PAK3*, a gene that has been linked with learning difficulties [Willatt 2005]. 196466728-196559518

ZDHHHC19 may be linked with learning difficulties. Changes in a related gene [*ZDHHHC9*] cause learning difficulties [Goobie 2008]. 195924320-195938308

There is interest in identifying the gene or genes responsible for certain features of a 3q29 microduplication or duplication and doing so may help to guide future studies, but this does not lead directly to immediate improved treatment. Even if an extra copy of the supposedly responsible gene is present, the associated feature[s] will not necessarily be present. Other genetic and environmental factors are often important as well.



How did this happen?

Most 3q29 duplications occur out of the blue. The genetic term for this is **de novo** (dn) (see page 4). By contrast, most typical 3q29 microduplications are inherited from the mother (mat) or the father (pat). A blood test to check the parents' chromosomes will show what the situation is [Ballif 2008].

De novo 3q29 duplications are caused by a mistake that occurs when the parents' sperm or egg cells are formed or else very shortly after conception, when a baby is made. At one point in the formation of the sperm and egg cells, all the chromosomes including the two chromosome 3s pair up and swap segments. To pair up precisely, each chromosome 'recognises' matching or near-matching lengths of DNA on its partner chromosome. However, throughout the chromosomes there are many lengths of DNA that are so similar that it is thought that mispairing can occur. Very similar lengths of DNA have been found at both ends of the extra piece in the typical 3q29 microduplication and it is quite likely that they have caused a mismatch. Although no-one has ever seen this happen, it is believed that when the next step – the exchange of genetic material, known as 'crossing over' – follows, it is unequal, looping out and adding the length of the chromosome that is gained in a typical 3q29 microduplication. Something similar may occur with larger duplications.

Whether the duplication is inherited or de novo, what is certain is that as a parent there is nothing you did to cause the 3q29 duplication and nothing you could have done would have prevented it from occurring in your child. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 3q29 duplication or any other chromosome disorder. Very rarely (less than 1%), both parents have normal chromosomes by a blood test, but a few of their egg or sperm cells carry the 3q29 duplication. This is called **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.

In families where the 3q29 duplication has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 3q29 duplication 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 3q29 microduplication have similarly affected children?

We have not known about the typical 3q29 microduplication for long enough to be certain if it affects fertility but it is likely that fertility will be normal. In each pregnancy, someone with the microduplication has a 50 per cent risk of passing it on and a 50 per cent chance of having a child without the microduplication.

References

Ballif 2008: Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication *Molecular Cytogenetics* April 28 1: 8
Ballif BC *et al.* **Free access**

Goobie 2008: Molecular and clinical characterization of de novo and familial cases with microduplication 3q29: guidelines for copy number variation reporting *Cytogenetic Genome Research* March Volume 123(1-4) pages 65-78 Goobie S *et al.*

Lisi 2008: 3q29 Interstitial Microduplication: A New Syndrome in a Three-Generation Family *American Journal of Medical Genetics Part A* Volume 164A Pages 601-609 Lisi EC *et al.*

Rooms 2006: Multiplex ligation-dependent probe amplification to detect subtelomeric rearrangements in routine diagnostics *Clinical Genetics* Volume 69 pages 58-64 Rooms L *et al.*

Rosenberg 2006: Array-CGH detection of micro rearrangements in mentally retarded individuals: clinical significance of imbalances present both in affected children and normal parents *Journal of Medical Genetics* Volume 43 (2) pages 180-186 Rosenberg C *et al.*

Willatt 2005: 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome *American Journal of Human Genetics* Volume 77 pages 154-160 Willatt L *et al.* **Free access**

Support and Information



Understanding Chromosome & Gene Disorders

Rare Chromosome Disorder Support Group,

The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support.

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

www.rarechromo.org/donate

Please help us to help you!

This information 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. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. It was compiled by Unique and reviewed by Dr Denise Batista, Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, USA and by Unique's chief medical advisor, Professor Maj Hultén BSc PhD MD FRCPath, Professor of Reproductive Genetics, University of Warwick, UK.

2011 version 1 (PM)

Copyright © Unique 2011