

Inform Network Support



Understanding Chromosome & Gene Disorders

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15q11.2 microdeletions

This leaflet is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. The information is believed to be the best available at the time of publication. It was compiled by *UniquE* and reviewed by Dr Charlotte von der Lippe, University of Oslo, Norway and by Professor Maj Hultén, Professor of Reproductive Genetics, University of Warwick, UK and chief medical advisor to *UniquE*. 2012.

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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 (<http://www.ncbi.nlm.nih.gov/pubmed>). If you wish, you can obtain most articles from *Unique*. In addition, this leaflet draws on information from a survey of members of *Unique* conducted in 2011, referenced *Unique*. When this leaflet was written *Unique* had 15 members with a 15q11.2 microdeletion. These members range in age from a child of three years to adults. There are 189 further people described in the medical literature. However, the majority (100/189) were diagnosed as a result of several large studies of people with schizophrenia or epilepsy and there is very little information available about most of these individuals (Mefford 2009; de Kovel 2010; Grozeva 2011; Stefansson 2011).

15q11.2 deletions

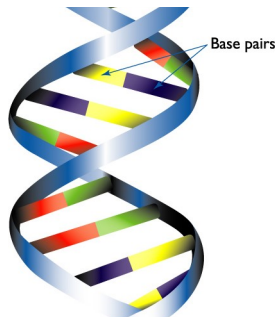
A 15q11.2 deletion is a very rare genetic variation in which there is a tiny piece of chromosome 15 missing. The deletion is found at a place called q11.2. Because the missing piece is very tiny indeed, you will sometimes see it called a microdeletion.

What we know about 15q11.2 microdeletions comes from studying people who have a reason for having a genetic test. The reason might be developmental delay, unusual behaviour or a health problem, or perhaps the 15q11.2 microdeletion has been found in someone else in their family. This gives us a biased sample. If we looked for the 15q11.2 microdeletion in the general population, we would have an unbiased sample, but it is very difficult to do. This means that at the moment we can't be sure about the effect of a 15q11.2 microdeletion. There is still a lot to learn, but this guide contains the best information we have to date.

The features of people with a 15q11.2 microdeletion vary widely, even among members of the same family. People can have developmental delay, learning difficulties and behavioural problems. However, many people with the microdeletion have no apparent physical, learning or behaviour difficulties.

What does the 15q11.2 microdeletion mean?

Chromosome 15 is one of the 23 pairs of chromosome in the cells of the body that carry genetic material. The top bit down to the indent on the diagram on the next page is known as p. The bottom bit is called q. Chromosomes are made up of DNA, which contains the genetic instructions for development and functioning. DNA has a ladder-like structure, with the ladder's rungs formed from chemicals known as base pairs. The size of the tiny bit of 15q11.2 missing is measured in base pairs. There are millions of base pairs on a chromosome so the numbers are usually shortened. One thousand base pairs are called a kilobase and is written as 1kb. One million base pairs are called a megabase and is written as 1Mb.



prevented it from occurring in your baby. No environmental, dietary or lifestyle factors are known to cause these chromosome changes. No one is to blame when this occurs and nobody is at fault.

Can it happen again?

Where both parents have normal chromosomes, it is unlikely that another child will be born with a 15q11.2 microdeletion 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 15q11.2 microdeletion. 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 deletion.

In families where the 15q11.2 microdeletion has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the 15q11.2 microdeletion rises to 50% in each pregnancy. However, the effect of the microdeletion 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.

Notes

Adults with 15q11.2 microdeletions

Several adults have been described in the medical literature and *Unique* has two adult members with the microdeletion. Both *Unique* members and some adults in the medical literature have no developmental delay or health issues and only discovered they carried the microdeletion after their child was diagnosed. A number of parents in the medical literature passed the microdeletion on to their children; three of whom had learning difficulties and one who was well-educated but described problems with interaction with other people from childhood. Two unaffected grandmothers discovered that they carried the microdeletion after a grandchild was diagnosed (Murthy 2007; Doornbos 2009; von der Lippe 2011; *Unique*).

Ongoing research involving 15q11.2

A 15q11.2 microdeletion is tiny, so it can only be found using molecular techniques such as microarrays (array-CGH) or targeted cytogenetic testing using FISH. These techniques show whether particular genes are present or not. The features of 15q11.2 microdeletion syndrome are likely to be a result of the loss of a number of different genes found in this region. The typical 15q11.2 microdeletion is 500kb and contains four genes: *NIPA1*, *NIPA2*, *CYFIP1* and *TUBGCP5* (see diagram on page 3). We don't yet know enough about what the function of these genes are and how having one copy of each of the missing genes leads to the features of having a 15q11.2 microdeletion. However, *CYFIP1* has been suggested to be involved in the increased risk of developing schizophrenia, and a deletion of *TUBGCP5* has been suggested to be likely to result in an increased risk for behavioural difficulties in these children (Doornbos 2009).

It is important to remember that while identifying the gene(s) responsible for certain features of the 15q11.2 microdeletion 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 missing it does not always mean that the associated feature(s) will be present. Other genetic and environmental factors often have a role in determining the presence or absence of a particular feature.

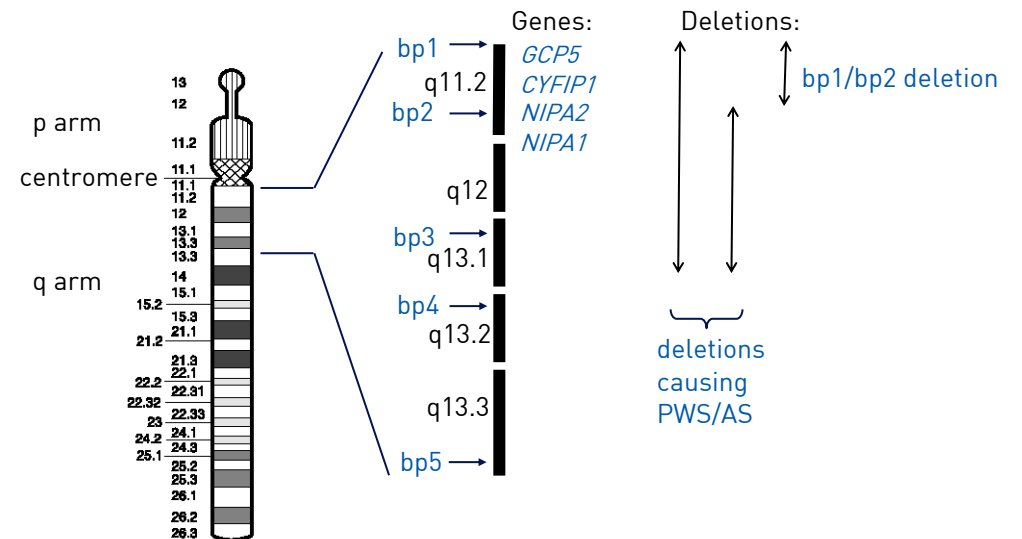
Why did this happen?

A blood test to check both parents' chromosomes is needed to find out why the 15q11.2 microdeletion occurred.

A number of parents have been known to pass a 15q11.2 microdeletion on to their child (Murthy 2007; Doornbos 2009; von der Lippe 2011; *Unique*). However, in some cases so far the microdeletion occurred when both parents have normal chromosomes. The term that geneticists use for this is *de novo* (dn) which means 'new'. *De novo* 15q11.2 microdeletions are caused by a change that occurred when the parents' sperm or egg cells formed, or possibly during formation and copying of the early cells after the egg and sperm joined.

Whether the microdeletion is inherited or *de novo*, as a parent there is nothing you did to cause the 15q11.2 microdeletion and nothing you could have done would have

The 15q11.2 region of the long arm of chromosome 15 contains a number of **low copy repeats** (regions of repetitive DNA which are susceptible to rearrangements) known as breakpoint 1 (bp1), bp2, bp3, bp4 and bp5. 15q11.2 microdeletions refer to a typical 500kb (0.5Mb) deleted region located between bp1 and bp2. Larger deletions involving bp3 cause either Prader-Willi or Angelman syndrome (PWS/AS) depending on which parent the deleted chromosome is inherited from.



Array CGH report

The laboratory that finds the 15q11.2 microdeletion will send a report that is likely to read something like the following example:

arr[hg19] 15q11.2 (22765637-23217454)x1 (bp1bp2)

arr The analysis was by array-CGH
hg19 Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new "builds" of the genome are made and the base pair numbers may be adjusted

15q11.2 The chromosome involved is 15, band q11.2
(22765637-23217454)x1

The base pairs between 22765637 and 23217454 have been shown to be deleted. Take the first long number from the second and you get 451894 (452kb). This is the number of base pairs that are missing. x1 means there is one copy of these base pairs - not two as you would normally expect

bp1bp2 bp1 refers to breakpoint 1 and bp2 refers to breakpoint 2 (see diagram above). The region between breakpoints bp1 and bp2 is missing.

Emerging phenotype: what to expect

Because only very small numbers of people have been identified, we can't yet be certain what the full range of possible effects of the microdeletion are. Additionally, the features vary, even between members of the same family. They do not affect everyone and in any individual they can be more or less obvious.

The most common features are:

- Children may need support with learning. The amount of support needed by each child will vary, although most benefit from supportive services for special needs
- Behaviour and emotional disorders including attention deficit hyperactivity disorder and/or autism in some children
- Speech delay in some children

Are there people with a 15q11.2 microdeletion who have developed normally and have no speech, learning or health difficulties?

Yes, there are. Sometimes the 15q11.2 microdeletion can be silent. Some parents of children with a 15q11.2 microdeletion have the same microdeletion but do not have any obvious unusual features or delayed development (Doornbos 2009; Stefansson 2011; von der Lippe 2011; *Unique*).

The effect on development, health and behaviour of some genetic disorders ranges from being barely perceptible to being obvious and severe.

If one person in a family with the 15q11.2 microdeletion is mildly affected, will others in the same family also be mildly affected?

Not necessarily. There is a lot of variation between different members of the same family who have the same microdeletion. We know that if one person is mildly affected or unaffected, others may be more severely and obviously affected. There are two families described in the medical literature who have three generations with the microdeletion (Doornbos 2009; von der Lippe 2011; *Unique*).

What is the outlook?

We can't be sure yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan. Several adults have been described in the medical literature and *Unique* has two adult members (see page 9).

Pregnancy

Most mothers carrying babies with a 15q11.2 microdeletion experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. There is information available on 17 pregnancies of mothers carrying a baby with a 15q11.2 microdeletion. Twelve had no pregnancy problems and no unusual findings on ultrasound scans. Three babies had intrauterine growth retardation (IUGR). This is a term used to describe babies whose growth in the womb

diagnosis of autism can be extremely helpful in accessing services and tailoring educational and behavioural therapy to meet the specific needs of a child with autism. A third (20/59) of those in the medical literature are affected by tantrums, self-injury or obsessive compulsive disorder (OCD). OCD is an anxiety-related condition in which people experience frequent intrusive and unwelcome obsessional thoughts, often followed by repetitive compulsions, impulses or urges (Murthy 2007; Doornbos 2009; Burnside 2011; von der Lippe 2011; *Unique*).

A 24-year-old in the medical literature was diagnosed with Asperger's syndrome (an ASD that is characterised by significant difficulties in social interaction along with restricted and repetitive patterns of behaviour and interests) and psychosis (a condition that affects a person's mind and causes changes to the way that they think, feel and behave, and can result in an inability to distinguish between reality and imagination). He needs a firm structure in his daily life and reminders of what to do to cope with daily living. His 12-year-old brother, who also has a 15q11.2

microdeletion, has similar problems with social interaction, communication and concentration, and also needs a firm structure and predictability. He is described as having phobic anxiety reactions but he does not have psychosis (von der Lippe 2011).

Eighteen out of 69 people in the medical literature who have a 15q11.2 microdeletion are also affected by schizophrenia. Schizophrenia is a mental health condition that causes a range of different psychological symptoms, including hallucinations (hearing or seeing things that do not exist) and delusions (believing in things that are untrue). Schizophrenia can be treated using a combination of medical treatments such as antipsychotic medicines, and psychological interventions such as cognitive behavioural therapy. All of these people were diagnosed first with schizophrenia and discovered that they carried the 15q11.2 microdeletion when they took part in one of several large studies of people with schizophrenia. These studies also identified 59 out of 69 people who are not affected by schizophrenia but who have a 15q11.2 microdeletion. This suggests that the microdeletion of 15q11.2 is not sufficient (even in the same family) to cause schizophrenia but the microdeletion may increase the risk of developing schizophrenia (Mefford 2009; Stefansson 2011).

“ His favourite activities are playing music on his CD player and linking together extension cords to plug things in. He also enjoys watching animated movies and helping his parents cook. He likes routine and for things to be done in a certain order. If this is followed he has normal behaviour. He has obsessive compulsive tendencies and this causes difficulties when activities are done out of sequence. He can be very aggressive and is hyperactive. His social skills are not on the same level as other children his age. He was diagnosed with autism at the age of 27 months. He prefers to interact only with adults. Although he tolerates his peers, he does not seem to want to engage in activities with them. He likes to interact one-on-one and gets anxious in group settings. He receives ABA [applied behaviour analysis] therapy daily and this has been very successful at getting him to speak and become a part of his classroom. ” – 4½ years

“ He is friendly but he struggles with his peers. He is easy-going unless something doesn't go his way: he has a temper tantrum and it isn't easy to calm him down. He is emotionally immature. He has a temper tantrum a couple of times per week. ” – 5 years

incurving fifth finger (clinodactyly). Another child has joints that are hypermobile (Doornbos 2009; von der Lippe 2011; *Unique*).

One baby has microcephaly (a small head) and one has plagiocephaly (the back or side of the baby's head appears flattened) (Doornbos 2009).

Three babies were born with a cleft palate (an opening in the roof of the mouth) and one of these babies also had tracheolaryngomalacia (floppiness of the larynx, trachea or both) (Murthy 2007; Doornbos 2009).

One child had a multicystic dysplastic kidney (a condition in which the kidney has been essentially replaced by multiple cysts. It is the result of abnormal fetal development of the kidney and there is little or no normal function to this kidney). One teenager had kidney (urethral) reflux (urine flows upwards from the bladder back up to the kidney, potentially damaging the kidneys) as a child (von der Lippe 2011; *Unique*).

One child had a broad neck and pectus excavatum (a sunken chest) (Doornbos 2009). One child had 13 ribs and hypospadias (the hole that is usually sited at the end of the penis is on the underside instead) (Doornbos 2009).

One child had cryptorchidism (undescended testes). The testicles can be brought down by a straightforward surgical operation (Doornbos 2009).

One baby had an umbilical hernia (a soft skin-covered bulge at the belly button) (Doornbos 2009).

Other concerns

■ Breathing

Three children had frequent chest infections and one had asthma (Doornbos 2009; *Unique*).

■ Vision

Several people with the microdeletion have eye problems. Three children had a squint (where the eye turns inwards, outwards, upwards or downwards); one child is short sighted; one is long sighted; and one has entropion of the lower eyelids (the eyelids fold inwards) (Doornbos 2009; von der Lippe 2011; *Unique*).

■ Hearing

Three children have mild hearing loss due to recurrent ear infections; they all had grommets (a small ventilation tube) inserted into their eardrums. A teenager and an adult have a hearing impairment and have hearing aids (Doornbos 2009; von der Lippe 2011; *Unique*).

Behaviour

In general children with a 15q11.2 microdeletion are happy and affectionate. Children with a 15q11.2 microdeletion seem to be more likely to have attention deficit hyperactivity disorder (ADHD), which is characterised by restlessness and a short attention span. ADHD has been reported in the medical literature to affect around a third (21/59) of those with the microdeletion and has also been reported in *Unique* members with the microdeletion. Autistic traits or autistic spectrum disorder (ASD) have also been reported in almost a third (19/59) people with a 15q11.2 microdeletion in the medical literature and also in *Unique* members. A

has slowed, resulting in babies that are smaller than expected for the number of weeks of pregnancy. One mother had maternal hypertension (high blood pressure). One baby had an increased nuchal translucency at a first trimester screening scan. Nuchal translucency is a measurement of the collection of fluid under the skin at the back of the baby's neck. An increase in the amount of fluid indicates an increased risk that the baby has a chromosome disorder. The mother chose to have the prenatal diagnostic test chorionic villus sampling (CVS) test which did not detect the microdeletion (because the deletion is so small) but a heart defect was later detected at the 20 week ultrasound scan. Another baby was delivered two weeks early due to the mother's placental failure (the placenta was not providing the unborn baby with enough nutrients). Another mother had oligohydramnios (too little amniotic fluid) (Murthy 2007; Doornbos 2009; von der Lippe 2011; *Unique*).

Feeding and growth

Feeding difficulties do not appear to be common. However, five babies had feeding problems as babies or infants; two of whom were tube fed until the age of 12 months and 18 months. Another had swallowing problems which were resolved at 1 year by eating therapy (Doornbos 2009; *Unique*).

The majority of children do not seem to have any growth problems and are of normal height and weight, although three children have been described as short or small (Doornbos 2009; von der Lippe 2011; *Unique*).

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

Often gross motor skills are unaffected in those with a 15q11.2 microdeletion, although 44 percent (29/66) of children in the medical literature and two children at *Unique* are described as having motor delay, which means that it may take a little longer for children to roll over, sit, crawl and walk. Children often benefit from physiotherapy. Some children have an unusual gait when they walk or have problems with co-ordination (Murthy 2007; Doornbos 2009; Burnside 2011; *Unique*).

Around 20 per cent (13/67) of children in the medical literature and six at *Unique* have hypotonia (low muscle tone or floppiness) (Murthy 2007; Doornbos 2009; Burnside 2011; *Unique*).

“ He sits, walks, climbs stairs, runs, skips and gallops. His favourite activity is to jump on the trampoline. ” – 4½ years

“ He has muscle weakness on the left side of his body. He walks but he is clumsy, and struggles with steps but can climb them. He can barely jump and can't pedal a standard bicycle but can pedal a trike. He gets physical therapy once a week at school and does the recommended exercises at home. ” – 5 years

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

Fine motor skills may be affected in some children, which means they may take longer to reach for and grab toys and hold a bottle or cup. Some children have occupational therapy to try to help overcome these difficulties (von der Lippe 2011; *Unique*).

“ He was unable to hold his bottle until after his first birthday. He was almost 15 months before he was able to hold and drink from a sippy cup. He also had a difficult time using utensils - not fully mastering this until after his third birthday. His self-care skills (toilet training and dressing himself) are not age appropriate, as he is still not fully toilet trained and has a hard time dressing himself. ” – 4½ years

“ He is fully toilet trained (day and night) and never wets the bed. He can brush his teeth by himself and put on his shoes on the correct feet. He does not have a good pencil grip, but it has improved through classes at school. ” – 5 years

Delay in starting to speak and language development

Some, although not all, children with a 15q11.2 microdeletion have a delay in acquiring speech and language skills. Among *Unique* members a 3½-year-old has speech delay and is about one year behind; a 4½-year-old had expressive speech delay which has improved over time and he is now fully verbal and uses full sentences; a 4½-year-old is non-verbal; a 5-year-old speaks but is still behind his peers; a 6-year-old has speech delay and speech therapy; and a 9-year-old is fluent in two languages and has no speech delay. In the published medical literature 92 percent were described as having delayed speech, with children not speaking in sentences until the age of 6 to 8 years. An 11-year-old boy had articulation difficulties and needed speech therapy. Before learning to speak he used PECs and signing to communicate (Doornbos 2009; Burnside 2011; von der Lippe 2011; *Unique*).

There are many reasons for the speech delay, including the link between the ability to learn and the ability to speak.

“ He did not speak until he was almost 3 years old, but has made great improvements since receiving speech therapy. Before he was verbal he used PECs and signing, which was successful. He now speaks in sentences. ” – 4½ years

“ He started talking at 19 months and uses 4 or 5 word phrases. He is behind his peers and stutters on occasion, and struggles talking when he is excited or upset. ” – 5 years

Learning

At least 38 people described in the medical literature or members at *Unique* have no learning difficulties. However, there are people with a 15q11.2 microdeletion both in the medical literature and known to *Unique* who have learning difficulties and there is a broad spectrum of need for support with learning. Two people are described as having borderline learning difficulties; four people as having mild learning problems and one has a moderate learning difficulty. Fifteen further individuals are described more generally as having learning problems. Many children with a learning difficulty benefit from attending a special educational school and/or having 1:1 assistance in the classroom (*Unique*).

One father who passed the microdeletion on to his son described himself as ‘not very good at school’ and struggled particularly with reading. His 11-year-old son was

diagnosed after having difficulties with reading and writing. A mother also had difficulties with reading and writing. Two people are described as having memory problems (Murthy 2007; Doornbos 2008; de Kovel 2010; von der Lippe 2011).

“ He is very intelligent and appears to be intellectually equal, if not slightly above his peers. He has a terrific memory and is very loving and happy most of the time. ” – 4½ years

“ He has delays in his learning but his memory seems good. He cannot read but can draw a basic face. He loves to do puzzles, look at books, drawing, crafts and board games. ” – 5 years

Increased risk of developing seizures

Seizures (epilepsy) appear to affect around 27 per cent (24/90) of those with a 15q11.2 microdeletion. One study found that 12 out of 18 people (from five families) with the microdeletion had seizures. In four of these families the person having the seizures inherited the microdeletion from a parent who did not have seizures. In three families, a parent who did not have the microdeletion did have seizures. This suggests that the microdeletion of 15q11.2 is not sufficient (even in the same family) to cause epilepsy but the microdeletion may increase the risk of developing seizures (Doornbos 2009; de Kovel 2010; Burnside 2011; *Unique*).

Some babies with a 15q11.2 microdeletion are born with a birth defect. Others are not. Birth defects can affect any organ in the body: there doesn't seem to be any consistent pattern

Many babies with a 15q11.2 microdeletion are born completely healthy. Others have a birth defect which can be quite minor or more serious. Most of the birth defects reported among babies with a 15q11.2 microdeletion have only occurred in just a few babies, so they may be a coincidence, and it is still not clear if any of the birth defects reported here are actually caused by the 15q11.2 microdeletion.

In two babies in the medical literature the heart was affected. One child had a ventricular septal defect (VSD; a hole in the wall between the two pumping chambers of the heart called the ventricles). Another child has an atretic pulmonary valve (the valve which is normally located between the right ventricle and the pulmonary artery is abnormal and doesn't open). This means that oxygen-poor (blue) blood can't flow forward from the right ventricle to the lungs to get oxygenated. The failure of the pulmonary valve to develop can also result in a small (or missing) right ventricle that can't adequately pump blood to the lungs. No members of *Unique* have reported a heart defect (Doornbos 2009).

Children and adults with the microdeletion may have hands and/or feet that are not perfectly formed. Two children were born with clubfeet. One child has long toes. One child has swan neck deformities in several fingers (the joint closest to the fingertip is permanently bent toward the palm, while the nearest joint to the palm is bent away from it). This child also has contractures (loss of joint movement) in their elbows, wrists and fingers and has juvenile arthritis (joint inflammation). Another has an