

UNIQUE
UNDERSTANDING GENES & CHROMOSOMES

2p16.3 (NRXN1) deletions

rarechromo.org



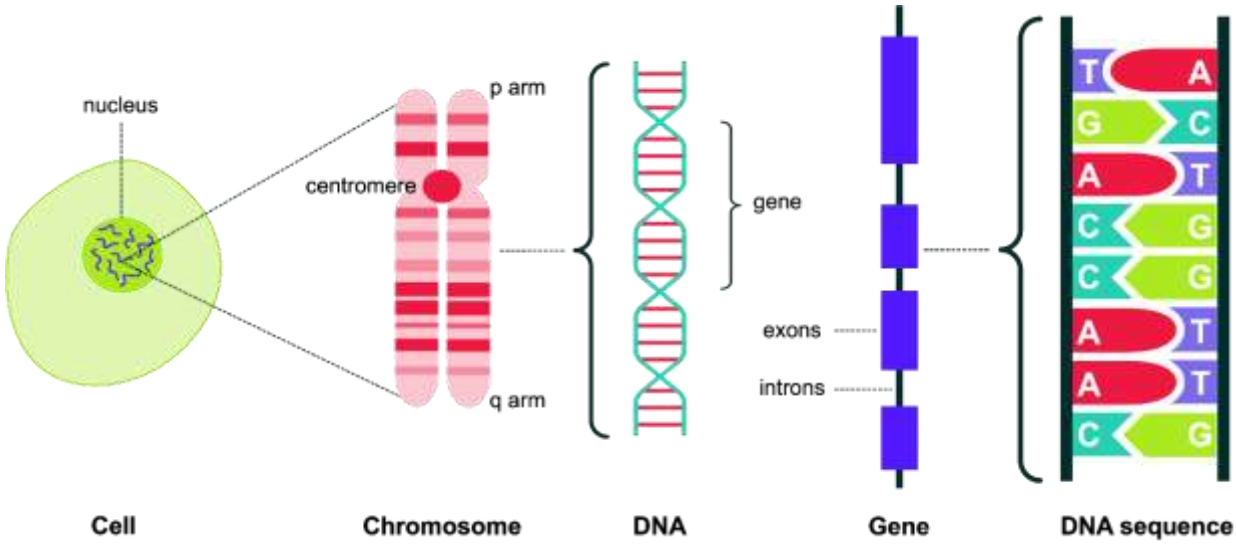
This guide is designed to help families and healthcare professionals looking after people with a 2p16.3 (NRXN1) deletion. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this condition.

2p16.3 (NRXN1) deletions

A 2p16.3 deletion is a rare genetic condition caused by a tiny missing part of one of the body's 46 chromosomes – chromosome 2. For healthy development, chromosomes should contain just the right amount of material – not too much and not too little. Even a tiny piece of missing material can disrupt development, although it doesn't always do so.

Background on chromosomes

Chromosomes are structures found in the nucleus of most of the body's cells. Every chromosome contains thousands of **genes** which may be thought of as individual instruction booklets that contain the genetic information telling the body how to develop, grow and function. Chromosomes (and hence genes) consist of a complex chemical called **DNA**. Chromosomes usually come in pairs, with one half of each chromosome pair being inherited from each biological parent. Humans have 23 pairs of chromosomes giving a total of 46 individual chromosomes. Of these 46 chromosomes, two are the sex chromosomes. Females usually have two chromosomes X and males usually have one X chromosome and one Y chromosome. The remaining 44 chromosomes are grouped in 22 pairs, numbered 1 to 22, approximately from the largest to the smallest. Each chromosome has a short or petit (p) arm and a long (q) arm.

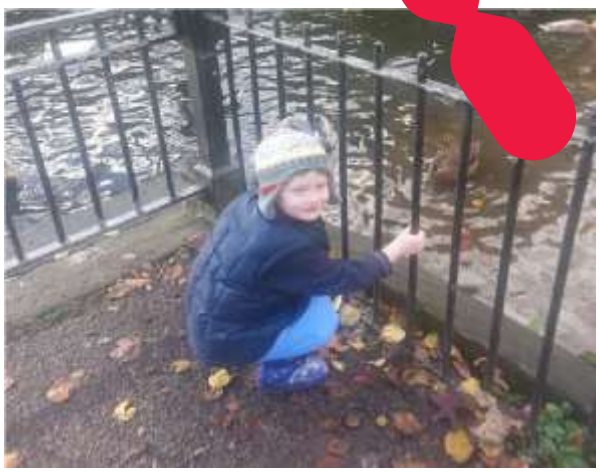


What causes 2p16.3 (NRXN1) deletions?

Sperm and egg cells contain one copy of each chromosome. When children are conceived, a sperm cell from the father and an egg cell from the mother join together to form a single cell that now carries two copies of each chromosome. This cell must make many copies of itself (and all the chromosomes and genetic material) in order to make all of the many cells that form during human growth and development. Sometimes during the formation of the egg or sperm cells or during this complicated copying and replication process, parts of the chromosomes can break off or become arranged differently from usual. People with a 2p16.3 microdeletion have one regular intact chromosome 2, but a piece from the short arm of the other copy is missing. It is believed that most of the clinical difficulties and other features associated with 2p16.3 deletions are caused by having only one copy (instead of the usual two) of a gene (or number of genes) from the missing piece. It is important to keep in mind that a child's other genes, environment and unique personality also help to determine future development, needs and achievements.

Looking at 2p16.3

You can't see chromosomes with the naked eye, but if you stain them and magnify them under a 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 chromosome 2 at the bottom of the page. DNA has a ladder-like structure, with the ladder's rungs formed from chemicals known as base pairs.



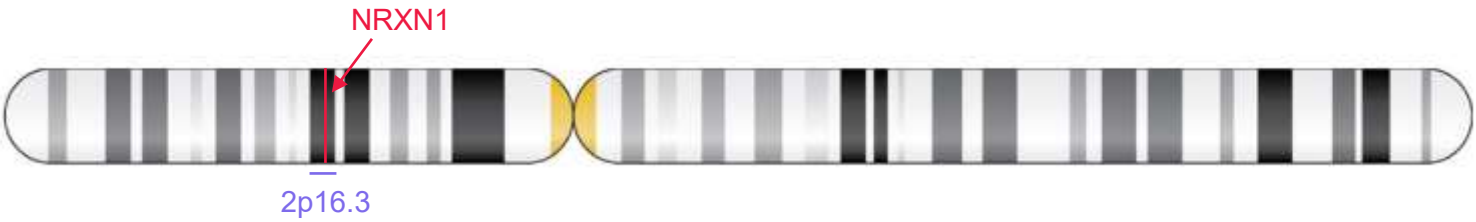
There are millions of base pairs in a chromosome, so the numbers are usually shortened. One million base pairs is called a megabase and written as 1Mb. Band 2p16.3 contains around 5.1 million base pairs (5.1Mb). This sounds a lot, but it is actually quite small and is less than 0.2 per cent of the DNA in each cell and only 2 per cent of the DNA in chromosome 2.

Even if you magnify the chromosomes as much as possible, to about 850 times life size, a chromosome 2 with the microdeletion at p16.3 often looks unchanged. People who have missing material on a chromosome are said to have a deletion, but when the amount is so small that it can't be seen even under a high-powered microscope, it is called a **microdeletion**. The 2p16.3 deletion can typically only be found using molecular or DNA technology, in particular a technique using microarrays (**arrayCGH**), that shows gains and losses of tiny amounts of DNA throughout the genome and can demonstrate whether particular gene(s) are present or not (Unique has prepared a guide to array CGH which can be freely downloaded from the Unique website). Nowadays, microdeletions of 2p16.3 are also frequently detected by exome or genome sequencing (Unique has a guide to **DNA sequencing**).

Unique publishes a separate guide to deletions and microdeletions

2p16.3 microdeletions are associated with developmental delay and behavioural concerns. One gene, called **Neurexin 1** (NRXN1), is located in band 2p16.3, and has been suggested to be responsible for most, if not all, of the features of 2p16.3 deletions (see Research involving 2p16.3). This guide includes descriptions of people who have a 2p16.3 microdeletion and people who have a full or partial deletion of the NRXN1 gene.

Chromosome 2



unique

Genetic Report

Your geneticist or genetic counsellor should be able to tell you about the points where the chromosome has broken in your child's case and so which base pairs of the chromosome are missing (deleted). With a 2p16.3 microdeletion, the results are likely to read something like the following example:

arr[hg19] 2p16.3 (50,713,464_51,043,557)x1 dn

arr — The analysis was by array (arr) comparative genomic hybridisation (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

2p16.3 — The chromosome involved is 2 and the position of the deletion is in band p16.3

50,713,464_ 51,043,557 — The base pairs between **50,713,464** and **51,043,557** have been shown to be deleted. Take the first long number from the second and you get 330,093 (0.330Mb or 330kb). This is the number of base pairs that are deleted

x1 — Means there is one copy of these base pairs, not two – one in each chromosome 2 – as you would usually expect

dn — Means de novo. The parents' chromosomes have been checked and no deletion or other chromosome change has been found at 2p16.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child. If instead of "dn" the report says "**mat**", this means that the deletion has been inherited from the biological mother; "**pat**" would mean that it has been inherited from the biological father.

Unique publishes a separate guide to Interpreting genetic test results

How common is a 2p16.3 deletion?

It is surprisingly common, almost certainly found as often as much better-known syndromes such as Prader-Willi. Several large-scale studies have shown that the 2p16.3 microdeletion occurs in around 1 in 2,500 to 1 in 4,000 people with schizophrenia or developmental delay; and about 1 in 5,000 people not affected by schizophrenia or developmental delay (Kirov 2008; Ching 2010; Schaaf 2012).

How much do we know?

Comparing different children and adults with a 2p16.3 (NRXN1) deletion shows that some effects seem to be very broadly similar. This information guide tells you what is known about those effects. Comparing your child's array results with others, both in the medical literature and within Unique, can help to build up a general picture of what to expect. But there will still be differences, sometimes quite marked, between your child and others with an apparently similar array result. It is very important to see your child as an individual and not to make direct comparisons with others with the same chromosome test results. After all, each of us is unique.

Most common features

Every person with a 2p16.3 (NRXN1) deletion is unique and so each person will have different medical and developmental concerns. Additionally, no one person will have all the features listed in this information guide while, when present, a feature can be more or less obvious. However, several common features have emerged:

- Children are likely to need support with learning. The amount of support needed by each child will vary
- Seizures
- Speech and language delay
- Behaviours and diagnoses such as an autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) disorder
- Most children are otherwise generally healthy.

What is the outlook?

A 2p16.3 (NRXN1) deletion will not resolve by itself and currently there is no cure. However, knowing the diagnosis means that appropriate monitoring and interventions can be put in place. Overall, life expectancy does not seem to be decreased.

Does everyone with a 2p16.3 (NRXN1) deletion have these features?

There are many individuals with either a deletion or disruption to the NRXN1 gene who have no obvious unusual features or delayed development, and no major health conditions present from birth, all of whom only discovered they had the deletion when it was detected in their children, or they were a control (unaffected) individual in one of the large-scale studies. Both fathers and mothers have passed the microdeletion on to their children (Dabell 2012; Béna 2013; Vinas-Jornet 2014; Sciacca 2022; Unique).

Will members of the same family with the same deletion be affected in the same way?

Not necessarily. There is a lot of variation between different members of the same family who have the same microdeletion. For example, we know that if one person is mildly affected or unaffected, others may be more severely and obviously affected (Kirov 2008; Ching 2010; Dabell 2012; Schaaf 2012; Béna 2013; Sciacca 2022; Unique).

Pregnancy and birth

Many pregnancies for babies with an NRXN1 deletion are uncomplicated and babies are born on or near their expected due date. Pregnancy complications in mothers carrying babies with NRXN1 deletions have been recorded for some, such as premature birth or pre-eclampsia, but no specific association with pregnancy complications or difficulties with delivery have been reported. Many babies show no signs of an NRXN1 deletion on ultrasound scans, and it is only discovered they are affected after birth. A few Unique babies spent time in NICU after birth.

First signs and age at diagnosis

The age of diagnosis can range from before babies are born after anomalies are detected on a prenatal ultrasound scan (Dabell 2012), to adults diagnosed after their own child is diagnosed (Schaaf 2012; Unique). For many children, the first signs of a 2p16.3 (NRXN1) deletion are delays in reaching developmental milestones such as sitting and moving or speech. Others have been diagnosed due to learning or behavioural concerns.

Unique publishes a separate guide to After Diagnosis: What Happens Next? (General guide)

> ***Concerns were first raised by about 15 months when he still showed no interest in walking or talking."***

"He showed slow development in usual milestones, delayed walking and speech and gross motor, hypotonia, hard to feed, sensory oral issues."

Feeding and growth

Feeding and growth are often not affected in children with a 2p16.3 (NRXN1) deletion. Most children with a 2p16.3 (NRXN1) deletion have expected growth, although a few have been reported to have faltering growth or poor weight gain (Ching 2010; Waterman 2012; Béna 2013; Vinas-Jornet 2014; Unique).

A few babies have been reported to have feeding difficulties. Hypotonia (low muscle tone) is common in babies with a 2p16.3 (NRXN1) deletion, and can lead to difficulties with sucking and swallowing, and/or latching onto the breast. The floppiness can also affect their food pipe and contribute to gastro-oesophageal reflux (in which feeds return readily up the food passage). Gastro-oesophageal reflux can generally be well controlled by giving feeds slowly, positioning a baby semi-upright for feeds, and where necessary raising the head of the end of the bed for sleeping. Feed thickeners and prescribed medicines to inhibit gastric acid may control reflux. Some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Unique). It is also possible to have a nasogastric tube (NG-tube passed up the nose and down the throat) or a gastric tube (G-tube; feeding directly into the stomach).

A few Unique children have features of an oral sensory issue, such as food colour aversion and gagging. Several have chronic constipation.

Unique publishes a separate guide to Feeding

> ***He was breastfed for the first 4 months. Eating is fine, a little fussy with some foods which may be sensory. Can only drink from a bottle, dribbles a lot from cups."***

"He was breastfed till 4 months, no issues feeding."

Motor skills (sitting, moving, walking)



Children with a 2p16.3 (NRXN1) deletion often have mild delays in learning to sit and walk. Many children, although not all, are delayed in reaching their motor milestones, which means it may take a little longer for them to roll over, sit, get moving and walk. From the information that is available, sitting unaided is often mastered between 6 and 18 months (at an average of 9 months) and walking is often mastered between 10 months and 3 years (an average of 19 months) (Ching 2010; Schaaf 2012; Unique).

One of the causes of the delay in mobility in children with a 2p16.3 (NRXN1) deletion is hypotonia (low muscle tone), which has been reported in around a third of children. This makes a child or baby feel floppy to handle but generally improves and may disappear with physiotherapy and exercises (Ching 2010; Schaaf 2012; Béna 2013; Unique).

"We found that slinging him has worked wonders. Rather than a pram he was carried in fabric slings from a very young age and these have been a useful tool to calm him and also to restrain him without seeming to restrain him as it's an enjoyable thing for him. He is now very active and needs to have a good run around each day to burn his energy off. Outdoors is where he loves to be. He was late to start sitting up and walking but can now do both easily and with much more stamina than his peers. He climbs stairs typically. He does not seem to want to use equipment like climbing frames, possibly because they require him to be careful! He does struggle a lot with physical boundaries – he has no sense of danger and will run into a road if not stopped. He loves walks outdoors, feeding the ducks etc but we have trained him to always hold hands or else he has a habit of bolting off which can be very dangerous." - 3 years 11 months

"He can't walk, stand or crawl. He is unable to put himself into a seated position and when placed in one he sits up for a very short time before lying back down. He enjoys being spun and going on swings. He is carried indoors and uses a buggy outdoors." - 4 years

"He is very active and physical!" - 7 years

"He does judo, horse riding, hockey, rides a scooter and bike, uses trampoline, loves running and swimming." - 9 years

"He is mobile and can climb. Can drop down at any time and sit... Loves to swing and bounce on trampoline and gym ball." - 9 years

Fine motor skills and self-care

Fine motor skills may be affected in children with a 2p16.3 (NRXN1) deletion. Hypotonia can also affect fine motor skills in children with a 2p16.3 (NRXN1) deletion and they may take longer to reach for and grab toys and hold a bottle or cup. This can lead to delays in children being able to self-feed, dress themselves (zips and buttons can be especially problematic) and hold a pen to write or draw. Special chunky cutlery, cups with handles, and cutting up food have helped some children. For those children who have problems holding and controlling a writing implement, mastering a keyboard or touch screen computer can often be easier (Waterman 2012; Unique). Toilet training may also be affected (Unique).

He has struggled with cutlery – only now at almost 4 does he confidently use a spoon and fork. He does not know how to use a knife. His fine motor skills are improving, it is mainly that he does not have the patience to sit and hold a pencil or count small beads. In the past six months he has become more independent and can carry a small plate of food and drink from a cup. He does enjoy using ICT [information and communications technology or computer] toys which involve lots of buttons to press such as my Tablet and touch screen games. Again, he is behind in this compared to his peers. He is in nappies at night and is slowly getting the hang of toilet training during the day. This is a slow process and has been going on for 2 months now. He enjoys baths, but does not wash independently. He will brush his teeth when supervised. He attempts to help by pulling his pants up for example when getting dressed but cannot get dressed on his own." - 3 years 11 months

"He struggles with buttons, laces, buckles and pencil grip. He has a gripper pen." - 7 years

"He finds it hard to do buttons. He had occupational therapy with good success. He cannot do buckles or laces on shoes." - 9 years

Learning

Children with a 2p16.3 (NRXN1) deletion often have learning disability. Many, although not all, children with an NRXN1 deletion require support with their learning. Of those children with learning (intellectual) disability, some will have mild or moderate learning disability, but some will have more severe learning disability. A child with learning disability is likely to need some learning support and many children benefit from attending a special educational school (Zahir 2008; Rujescu 2009; Wisniowiecka-Kowalnik 2010; Soysal 2011; Duong 2012; Schaaf 2012; Waterman 2012; Béna 2013; Vinas-Jornet 2014; Unique). Many children with an NRXN1 deletion have no learning disability and encounter no problems in school (Kirov 2008; Ching 2010; Dabell 2012).

Unique publishes separate guides to Education and Further education, training and work

He is around the 18 month-2½ year area on his EYFS [early years foundation stage] tracker. He has shown improvement since starting preschool. Physically he is at about his right age; this is his strongest area and also his imaginative play. He can make marks [on paper], but there's no apparent meaning ascribed to them." - 3 years 11 months

"He has a severe learning disability. He is in a special educational nursery with 1:1 support." - 4 years

"He has a mild learning difficulty. He is behind in reading and writing. He tests well if tested orally and has a pretty good memory. His more able areas of learning are anything physical." - 7 years

"He is up to grade with all subjects and 1 year ahead with spelling. He needs work on fluency. He has an amazing memory." - 9 years

"He has a severe to profound learning disability. He seems to remember places. Can recall tunes he would not have heard of for some time. He now has a 1:1 special needs assistant which is brilliant. Repetition helps him to learn." - 9 years

A number of children are hyperactive or described as being easily distractible or having a **poor concentration span**, which can make learning more of a challenge.

> ***He works to his own agenda. If it doesn't interest him, he refuses to give it any attention under any circumstances. His concentration is getting better - he can focus on an activity for 20 minutes now if it grabs his attention." - 3 years 11 months***

"He finds it hard to focus and follow 2-3 step directions." - 7 years

A Unique parent was asked: What helps your child to learn?

> ***A calm atmosphere, familiar faces and small groups – he gets overwhelmed with larger groups and his behaviour deteriorates. Sensory activities – especially outdoors. Calm repetition and lots of praise for good behaviour."***

Speech and communication

Speech and language delay is common in children with a 2p16.3 (NRXN1) deletion. Speech and language development is delayed in many, but not all, children with a 2p16.3 (NRXN1) deletion (Wisniowiecka-Kowalnik 2010; Béna 2013; Castronovo 2019; Ching 2010; Shehhi 2019). First words may emerge between 6 months and 6 years (average 2 years and 3 months) (Schaaf 2012; Unique) but some children are non-verbal. Some children may have a stutter. Children may find sign language or picture exchange communication systems (PECs) beneficial to help communicate their needs and wants. Unique families recommend **speech therapy**; one family recommends the Hanen programme, a programme aimed at promoting language, social and literacy skills, (hanen.org).

It is possible for speech and language delay to occur in children who have otherwise typical development and no learning disability (Béna 2013). There are many reasons for speech delay, including the link between the ability to learn and the ability to speak. The hypotonia experienced by many children results in weakness in the mouth muscles which in addition to insufficient sucking, can also affect the development of speech.

Unique publishes a separate guide to Communication

> ***He has a mix of words, gestures, pulling hands, PECS. Lots of shouting and random noises. First words were at about 2 years and 3 months. He uses two words, sometimes three at a push. Mainly nouns so he can name what he wants – 'Juice', 'biscuits'. He understands more than he can say. He uses PECS at nursery." - 3 years 11 months***

"He has no speech; vocal noises only." - 4 years

"He is verbal and started using words at the age of 2. He uses full sentences but is working on articulation." - 7 years

"He is verbal. He used PECS and basic signs and had weekly speech therapy (although not now)." - 9 years

"He has some PECS. Not pointing yet. Will pull you to what he wants. He uses single words infrequently. He can imitate tone and is currently saying more single words." - 9 years

Behaviour

Some children with a 2p16.3 (NRXN1) deletion have diagnoses such as an autism spectrum disorder (**ASD**) or attention deficit hyperactivity disorder (**ADHD**). Children with a 2p16.3 (NRXN1) deletion are often described as having a happy, charming and social personality.

A significant number of children – although not all – show a similar pattern of behaviours. It has been suggested that around two thirds of people with a 2p16.3 (NRXN1) deletion have a diagnosis of ASD or show autistic traits (Schaaf 2012). ASD is a condition that affects social interaction, communication, interests, and behaviour. A 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.

Some children have been reported with sensory integration (processing) disorder (a range of difficulties with taking in, processing, and responding to sensory information about the environment and from within one's own body) and a few children have been described as having no sense of danger (Schaaf 2012; Unique). ADHD, hyperactivity or attention problems have also been reported (Ching 2010; Dabell 2012; Schaaf 2012; Vinas-Jornet 2014; Unique). Poor concentration and fidgety behaviour seem to be an issue for quite a few children (Ching 2010; Unique).

Several children and adults have been described as having anxiety (Wisniowiecka-Kowalnik 2010; Vinas-Jornet 2014). A few children have self-injurious behaviour and one can also be aggressive (Béna 2013; Unique).

Unique publishes a separate guide to Challenging Behaviour

He loves animals, especially dogs. He plays well with ICT toys and cause and effect toys – e.g. hitting balls into a hole with a hammer for immediate gratification. He enjoys the company of family and is very physical – wants cuddles and kisses. He finds being cuddled in the sling very soothing – it has a similar effect I imagine to that of a weighted blanket. He does enjoy two TV programmes – 'Tree Fu Tom' and 'In The Night Garden'. He has two special teddies as well. He has displayed many behaviours that point to ASD and we are chasing this aspect up. We tend towards gentle discipline – telling him 'Kind Hands' when he lashes out or a firm 'No'. He reacts strongly to push against boundaries and needs lots of warning when an activity is ending or changing. He does not have obsessive routines as long as someone familiar is there. He is also very sensory led – loves to touch and feel with his whole body so is invariably in water play or rolling around in the mud. He will put anything in his mouth to taste at least once, including his own faeces. He also will not follow instructions and doesn't have any empathy for others. He is very much on his own agenda. He is fine with family but struggles to interact with other children – he pulls and pushes them to get their attention or hits them and doesn't understand why they get upset. He struggles to read facial expressions and body language and gets very frustrated and lashes out in anger." - 3 years 11 months

"He loves musical toys and people singing. He is a very happy boy, with the best giggle in the world." - 4 years

"He loves the dog, trampoline, swimming, judo, soccer, horse-riding, playing with brother, park, scooter, bike. He is a very sweet boy, loves brother, extremely active, very affectionate. He prefers smaller groups but is friendly." - 7 years

"He loves horse-riding, hockey, judo, swimming, running, loves school, enjoys walks with dog, park, swings. He is becoming more affectionate, very gentle, sensitive and nurturing. He is usually very well behaved but has ADHD and this can lead to fidgeting, anxiety and outbursts of frustration at times. He is socially a little behind, has plenty of peer friends, few close ones." - 9 years

"He loves cause and effect toys; his sister's dog; balls – to spin; the trampoline; swings and music. He does not like to be disturbed if engrossed in doing something; he needs plenty of warning that something is going to happen." - 9 years

Late-onset conditions

In a study of 501 people with Alzheimer disease (AD), 5 people were diagnosed with an NRXN1 deletion (Swaminathan 2011). Having an NRXN1 deletion may increase the chance of developing AD. AD is the most common cause of dementia. Dementia is a group of symptoms associated with a decline in the way your brain functions, affecting your memory and the way you behave.

There have been several large-scale studies of people with schizophrenia which have resulted in several (31/18,704 (0.17%)) people with schizophrenia being diagnosed with an NRXN1 deletion. Having an NRXN1 deletion may increase the chance of developing schizophrenia (International Schizophrenia Consortium IS 2008; Kirov 2008; Vrijnhoek 2008; Need 2009; Rujescu 2009; Duong 2010; Magri 2010; Vassos 2010; Levinson 2011; Stewart 2011; Levinson 2012; Sciacca 2022; Maury 2023).

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). The age of onset of the schizophrenia in people with an NRXN1 deletion is variable. Schizophrenia can be treated using a combination of medical treatments, such as antipsychotic medicines, and psychological interventions, such as cognitive behavioural therapy.

While it would therefore be recommended that families mention any concerns regarding mental health to a health professional, mental health concerns such as schizophrenia occur as the result of multiple physical, genetic, psychological and environmental risk factors, rather than just one single genetic difference such as a NRXN1 deletion. Carriers may therefore never develop any mental health conditions.

Sleep

Sleep problems do not seem to be common in children with a 2p16.3 (NRXN1) deletion, but some children have been reported to have sleep concerns (Béna 2013; Sciacca 2022; Unique).

Unique publishes a separate guide to Sleep

Appearance

Facial appearance

Children with 2p16.3 (NRXN1) deletions may have subtle facial features. Children may have a small head (microcephaly) or a large head (macrocephaly). Trained geneticists may recognise notable features but there do not seem to be any consistent specific features associated with this deletion (Béna 2013; Vinas-Jornet 2014; Unique).

Hands and feet

Minor hand and feet anomalies affect a few of those with a 2p16.3 (NRXN1) deletion and include incurving fingers (clinodactyly); differences of the thumb; uneven finger and toe lengths; bent little fingers (5th finger camptodactyly); tapering fingers; short fingers and/or toes (brachydactyly); clubfoot; curved second toes; flat feet; and high foot arches. Overall, the pattern is of variable minor hand and feet anomalies (Ching 2010; Soysal 2011; Waterman 2012; Béna 2013; Vinas-Jornet 2014; Unique).

Medical concerns

Seizures

Children with 2p16.3 (NRXN1) deletions have an increased risk of seizures. In a few studies, around 50 per cent (1 in 2) of those with a 2p16.3 (NRXN1) deletion were noted to have seizures (Schaaf 2012; Béna 2013). The seizure types are varied and there are several reports of the seizures being resistant to control with medication. Seizures affect less than 50 per cent of those at Unique and it appears that only a few of these children's seizures are not fully controlled with medication (Rujescu 2009; Ching 2010; Duong 2012; Schaaf 2012; Dabell 2013; Vinas-Jornet 2014; Sciacca 2022; Unique).

> ***He has absence epilepsy. His medication is good. To control the seizures, we try to minimise tiredness and flashing lights." - 7 years***

Joints

Joint laxity (looseness or instability of the joint, also called hypermobility or double jointedness) has been reported in some people. A few Unique members have stiff joints (Soysal 2011; Waterman 2012; Béna 2013; Unique).

Genital anomalies

Minor anomalies of the genitals are common in babies with chromosome disorders, most often affecting boys, including undescended testicles at birth (cryptorchidism). In a significant number of boys without any chromosome disorder, the undescended testes moves to the correct position in the scrotum within the next few months. Treatment for this condition is usually a combination of watchful waiting, with surgery to bring the testicles down if necessary (orchidopexy) (Béna 2013; Unique).

Eyesight

Eye anomalies or vision concerns have been very rarely reported in those with a 2p16.3 (NRXN1) deletion. These include several cases of Unique children who are long- (hypermetropia) or short-sighted (myopia). A few have a squint (strabismus) or involuntary eye movements (nystagmus).

Hearing

Generally, children have no hearing concerns. A few have been reported with a hearing loss (Dabell 2012; Schaaf 2012; Al Shehhi 2019; Unique). One child in the medical literature has hyperacusis (over-sensitivity to certain frequency and volume ranges of sound); a few Unique children are also hypersensitive to noise (Béna 2013; Unique). Young children sometimes have the fluctuating temporary hearing loss caused by a build-up of fluid behind the eardrum (glue ear), but they usually outgrow this naturally. If it is severe or persistent, tubes (grommets) may be inserted into the eardrum to aerate the space (the middle ear) behind it and improve hearing (Unique). Two Unique children have Auditory Processing Disorder (APD).

Unique publishes a separate guide to Hearing

Heart

Cardiac anomalies have been reported rarely. These have included a few children with a hole(s) in the heart, which either closed spontaneously or was corrected surgically (Ching 2010; Schaaf 2012; Unique).

Other health concerns

Other health concerns which may or may not be linked with the microdeletion (because they have only been reported very rarely) include osteogenesis imperfecta (brittle bone disease; a bone disorder where a person has brittle bones that are prone to fracture); scoliosis or kyphosis (curvature of the spine) (Soysal 2011; Schaaf 2012; Vinas-Jornet 2014; Sciacca 2022; Unique); anomalies in the cervical vertebra (neck) (Ching 2010; Unique); hip dysplasia (underdevelopment of the hip) (Ching 2010); a brain anomaly (Béna 2013; Unique); omphalocele (a type of abdominal wall defect in which the bowel, liver and other abdominal organs protrude out of the abdomen and into the base of the umbilical cord) (Schaaf 2012); pulmonary hypoplasia (underdevelopment of the lungs) (Schaaf 2012); and a diaphragmatic hernia (the diaphragm, a curved muscle that separates the contents of the chest from the abdomen, does not form completely, leaving a hole) (Bermudez-Wagner 2013).

Adults with a 2p16.3 (NRXN1) deletion

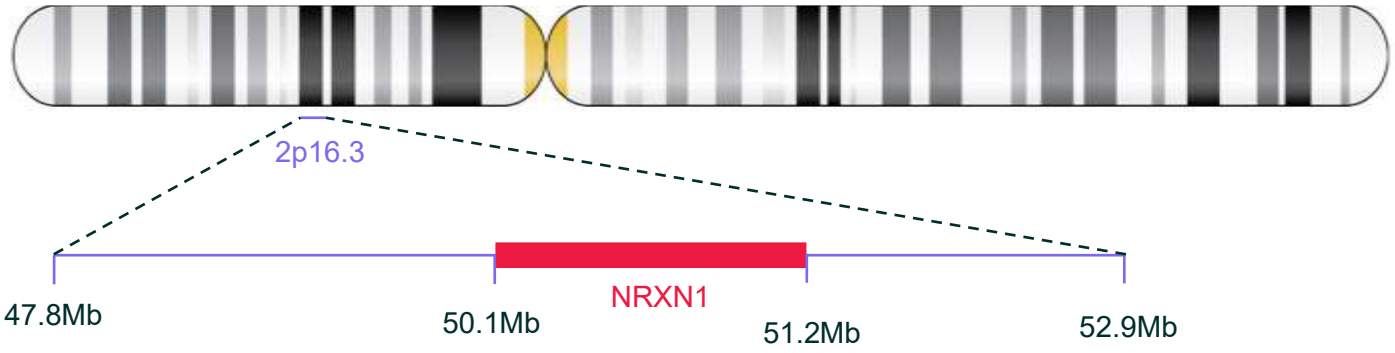
Several adults have been briefly described after their child was diagnosed. Most were unaffected by the deletion and had no developmental concerns. At least one parent is educated to degree level; another owns a successful company. However, parents who have passed on the deletion to their children include three mothers with learning disabilities and autistic features; one father who was treated for depression; a father with mild autistic features; one father with type 1 diabetes but who is otherwise healthy; a mother with bipolar disorder; a mother with a short attention span; and a father with learning disability and short stature. A 56-year-old man with severe learning disability lives in a group home (Dabell 2012; Béna 2013; Unique).

Unique publishes a separate guide to Transition

Research involving 2p16.3 and NRXN1

The microdeletion involving 2p16.3 can be as big as 5.5Mb; however, quite a few people have also been described in medical literature with either very small deletions, which contain only the NRXN1 gene, or a single base pair change (variant) within the NRXN1 gene itself. These people have a range of features very similar to those who have larger deletions, strongly suggesting that the NRXN1 gene may be the gene responsible for these features.

Chromosome 2



The numbers in this diagram refer to the human genome build 19 (hg19). 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.

The **NRXN1** gene codes for a protein called **Neurexin 1**. Neurexins are a group of proteins involved in ensuring the correct functioning of nerve cells (the building blocks of the nervous system). The nervous system is made up of the brain, spinal cord, and network of nerves in the body. This system controls everything a person does, including breathing, walking, thinking, and feeling. There are three neurexin genes (NRXN1, NRXN2 and NRXN3). NRXN1 located in 2p16.3 is one of the largest known human genes and is 1.1Mb in size.

It is important to remember that while identifying the gene(s) responsible for certain features of the 2p16.3 (NRXN1) deletion is valuable 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.

Deletion or disruption of both copies of NRXN1

We typically have two copies of each chromosome, and hence two copies of each gene. It is thought that the loss (or partial loss or disruption) of one copy of band 2p16.3 or NRXN1 makes someone more susceptible to learning disability, developmental delay and other features described in this guide.

However, it is also possible for both copies of 2p16.3 or NRXN1 to be affected. Those with both copies of 2p16.3 or NRXN1 disrupted or lost are more likely to be severely affected and usually experience the more severe forms of the features described in this guide. When both copies of NRXN1 are disrupted or missing it results in a Pitt-Hopkins-like syndrome (a syndrome which is characterised by learning disability and developmental delay, breathing problems and recurrent seizures) (Ching 2010; Gauthier 2011; Kasem 2018;

Castronovo 2020; Sciacca 2022; Ishizuka 2020). Those affected include five people described in the medical literature (one sibling pair and three unrelated people) who had lost both copies of NRXN1, all of whom were described as having severe learning disability and no speech, suggesting that losing both copies results in a person being more severely affected (Zweier 2009; Harrison 2011; Duong 2012; Béna 2013).

How did this happen?

In some cases, the 2p16.3 or NRXN1 deletion is inherited from a parent. In others, a blood test shows that both parents have regular chromosomes, and the deletion has occurred out of the blue for no obvious reason. The genetic term for this is **de novo** (**dn**). When children are conceived, the parents' genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. This happens naturally and is not due to anything a parent did or did not do. De novo 2p16.3 (NRXN1) deletions occur in this way when the parents' sperm or egg cells are formed or in the very earliest days after fertilisation.

What is certain is that there is nothing a parent could have done to prevent this from happening. No environmental, dietary or lifestyle factors are known to cause 2p16.3 (NRXN1) deletions. There is nothing that either parent did before or during pregnancy that caused the change. No one should be blamed for variants in their DNA and no parent is at fault when a new DNA change occurs in their child.

Can it happen again?

Where neither parent is found to carry the 2p16.3 (NRXN1) deletion, it is unlikely that another child will be born with a 2p16.3 (NRXN1) deletion or any other chromosome disorder. Very rarely, both parents have unaffected chromosomes by a blood test, but a few of their egg or sperm cells carry the 2p16.3 (NRXN1) deletion. Geneticists call this germline mosaicism, and it means that parents whose chromosomes appear unchanged when their blood is tested can have more than one child with the deletion.

Unique publishes a short general guide to Mosaicism

In families where the deletion has been inherited from a parent the possibility of having another child with the microdeletion rises to about 50 per cent (1 in 2) in each pregnancy.

If they wish, parents should have the opportunity to meet a genetic counsellor to discuss the specific chance of recurrence and options for prenatal and preimplantation genetic testing (PGT) for subsequent pregnancies. PGT requires the use of in vitro fertilisation and embryo biopsy, and only healthy, unaffected embryos are transferred to the mother's uterus. If the parents choose to conceive naturally, prenatal diagnosis options include chorionic villus sampling (CVS) and amniocentesis to test the baby's chromosomes. Testing is generally very accurate, although not all these tests are available in all parts of the world.

Unique publishes separate guides to Planning your next child, Prenatal genetic testing and diagnosis, A clinical genetics appointment and Supporting siblings of children with a rare genetic condition

Will my child have similarly affected children?

It is too early to know whether this deletion has any effect on fertility. However, there are quite a few reports of people with a 2p16.3 (NRXN1) deletion having children, so it is likely that fertility is unaffected. In each pregnancy, someone with the deletion is likely to have a 50 per cent (1 in 2) chance of passing it on and a 50 per cent chance of having a child without it. We haven't known about this microdeletion for long enough to be certain of the complete range of possible effects or how obvious they will be.

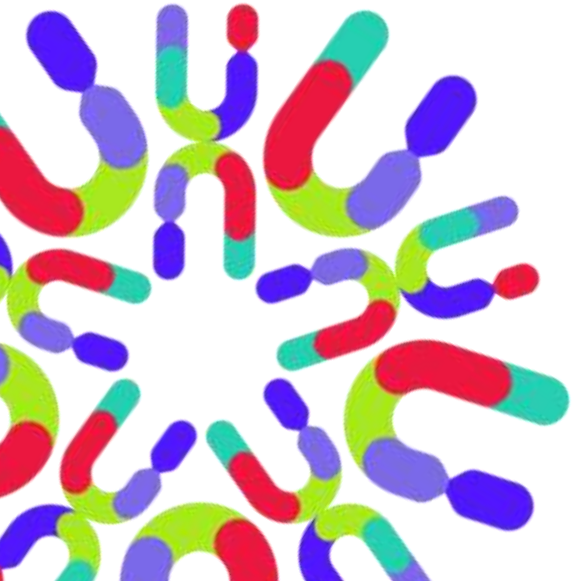
Families say...

> ***"He's been a 'child' for longer which has been lovely. He enjoys the very simple things in life and has shown us as a family that sometimes it's just enough to stop and have a cuddle at times. He is very affectionate and endearing despite his issues and manages to get everyone wrapped around his little finger!"***

Sources

The information in this guide is drawn partly from the published medical literature. The first-named author and publication date are given so you can look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain most articles from Unique. However, many individuals in the medical literature were diagnosed as a result of several large studies of people with autism spectrum disorder, epilepsy or schizophrenia and there is very little additional information available about these individuals.

In addition, this leaflet draws on information from a survey of members of Unique conducted in 2013, referenced Unique. When the original guide was written in March 2014, Unique had 25 member families with a microdeletion at 2p16.3. In 2024, an update based on medical literature and the Unique database was carried out. At this time, Unique had over 150 member families with a 2p16.3 microdeletion and 3 with an NRXN1 sequence variant (and no other recorded genetic change).



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

Websites and Facebook groups

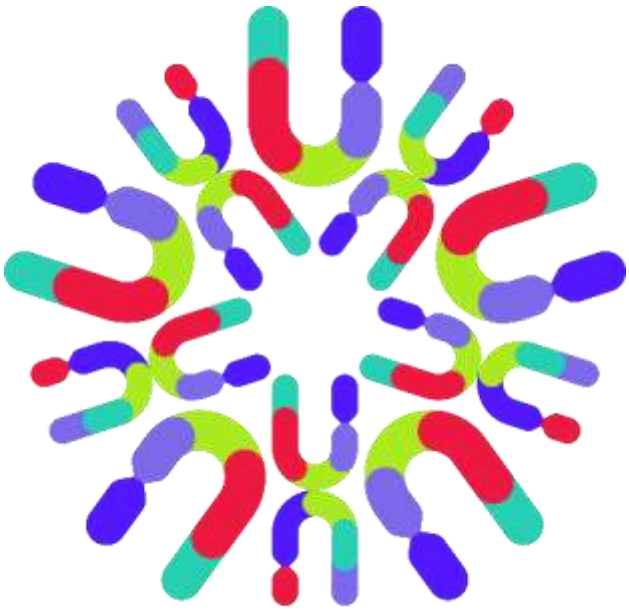
- **NRXN1: Simons searchlight community Facebook page**
- **The NRXN1 gene (Neurexin gene) for everyone Facebook page**
- **Chromosome 2p16.3 deletions and microdeletions Facebook page**
- **NRXN1 Network** – a patient advocacy group established by the mother of a child with a 2p16.3 (NRXN1) deletion

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. 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.

The original guide was compiled by Unique in 2014 and reviewed by Dr Christian Schaaf, Baylor College of Medicine, Houston, USA. The guide was updated based on medical literature and Unique's database by Unique (CA) and Chloe Pateman (Trainee Clinical Scientist) in 2024 and reviewed by Dr Christian Schaaf, Director and Chairman, Institute of Human Genetics, Heidelberg University Hospital, Germany. Rebranded 2026.

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