Understanding chromosome disorders

Unique

2p16.3 (*NRXN1*) deletions

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Sources and references

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 this guide was written in March 2014, Unique had 25 member families with a microdeletion at 2p16.3 ranging in age from a 3-year-old to an adult.

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 the body's cells. Every chromosome contains thousands of genes which may be thought of as individual instruction booklets (or recipes) that contain all the genetic information telling the body how to develop, grow and function. Chromosomes (and genes) usually come in pairs with one half of each chromosome pair being inherited from each parent. Humans have 23 pairs of chromosomes giving a total of 46 individual chromosomes. Of these 46 chromosomes, two are the sex chromosomes that determine gender. Females have two X chromosomes and males 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, shown on the diagram on page 3.

Chromosome Deletions

A sperm cell from the father and an egg cell from the mother each carries just one copy of each chromosome. When they join together they 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 deletion have one 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 are probably caused by having only one copy (instead of the

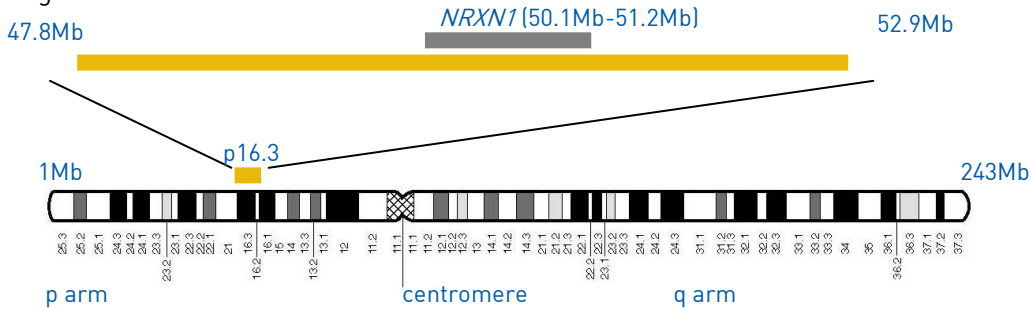
usual two) of a gene (or number of genes) from the missing piece. It is important to keep in mind that a child's other genes, environment and unique personality also help to determine future development, needs and achievements.

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 the long arm of chromosome 2 at the bottom on this page. Band 2p16.3 contains around 5.1 million base pairs. 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 on chromosome 2. Base pairs are the chemicals in DNA that form the ends of the 'rungs' of its ladder-like structure.

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

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 looks normal. 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 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 arrayCGH which can be freely downloaded from (www.rarechromo.org/information/Other/Array%20CGH%20QFN.pdf). One gene, Neurexin 1 (*NRXN1*) located on 2p16.3, has been suggested as being responsible for most, if not all, of the features of a 2p16.3 deletion (see Research involving 2p16.3 on page 16). This guide includes descriptions of people who have a 2p16.3 microdeletion and also people who have a full or partial deletion of the *NRXN1* gene.



Chromosome 2

The numbers in this diagram refer to the human genome build 19 (hg19; see page 4 for more details). Your child's report may refer to a different human genome build. Please contact Unique or your genetic specialist for any help with understanding the report.

Genetic Report

Your geneticist or genetic counsellor will be able to tell you about the points where the chromosome has broken in your child. 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 on each chromosome 2 – as you would normally 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. mat means that the deletion has been inherited from the mother; pat means that it has been inherited from the father.

How common is the 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 deletion 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 2p16.3 (*NRXN1*) deletions 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 of the features listed in this information guide. However, a number of 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
- Behavioural difficulties such as autism spectrum disorder
- Otherwise generally healthy

What is the outlook?

We can't be certain yet but there appears to be no reason why people who are healthy should not enjoy a normal lifespan. However, regression has been reported in three out of more than a hundred people in the medical literature (Schaaf 2012).

Are there people with a 2p16.3 (*NRXN1*) deletion who are healthy, have no major birth defects and have developed normally?

There are many individuals with either a deletion or disruption to the *NRXN1* gene who have developed normally and have no major birth defects, 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; Unique).

If one person in a family with the 2p16.3 (*NRXN1*) deletion 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 (Kirov 2008; Ching 2010; Dabell 2012; Schaaf 2012; Béna 2013; Unique).

Pregnancy and birth

Many pregnancies were uncomplicated and babies were born at or near their expected due date

Many mothers carrying babies with a 2p16.3 (*NRXN1*) deletion experienced no pregnancy problems, had a normal delivery and only discovered their baby was affected after the birth. However, pregnancy complications in mothers carrying a baby with a 2p16.3 (*NRXN1*) deletion have been reported. Three babies were born prematurely (before 36 weeks) (Ching 2010; Unique). One of these was delivered at 30 weeks due to the mother's pre-eclampsia (a sudden increase in blood pressure and the presence of excess protein in the urine. If left untreated, pre-eclampsia can have serious complications for both the mother and the baby). Three mothers had some bleeding during the first trimester (Unique). Three babies were diagnosed prenatally after anomalies were detected on a prenatal ultrasound scan (Dabell 2012).

First signs and age at diagnosis

For many children the first signs of 2p16.3 (*NRXN1*) deletion were delays in reaching developmental milestones such as sitting and moving or speech. Others were diagnosed due to learning or behavioural problems.

The youngest babies to be diagnosed were not yet born, and the oldest people were adults diagnosed after their child was diagnosed (Schaaf 2012; Unique).

> "Concerns were first raised by about 15 months when he still showed no interest in walking or talking." *Now 3 years 11 months*

> "He showed slow development in normal milestones, delayed walking and speech and gross motor, hypotonia, hard to feed, sensory oral issues." *Now 9 years*

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 normal growth, although a few have been reported to have faltering growth or poor weight gain (Ching 2010; Waterman 2012; Béna 2013).

The majority of birth weights recorded at Unique were within the normal range,

with an average of 3.278 kg (7lb 4oz) with only one baby with a low birthweight (below 2.6 kilos or 5lb 12oz) at term. Three other babies were born early (before 37 weeks) (Béna 2013; Unique).

Range of birth weights (at or near term):

2.438 kg (5lb 6oz) to 3.713 kg (8lb 3oz)

One baby was described as 'failure to thrive'. This term is used to describe a baby who has poor weight gain and physical growth failure over a period of time (Unique).

Feeding problems in babies have been reported for a few children. The hypotonia (low muscletone) that is common in babies with a 2p16.3 (*NRXN1*) deletion 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). This 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. If these measures are not enough, feed thickeners and prescribed medicines to inhibit gastric acid may control reflux, but some babies benefit from a fundoplication, a surgical operation to improve the valve action between the stomach and food passage (Unique). One baby at Unique benefited from having a nasogastric tube (NG-tube passed up the nose and down the throat) and later a gastric tube (G-tube; feeding directly into the stomach) which was removed at the age of 4 years (Unique). Another child has had feeding problems and has oral sensory issues (food colour aversion and gagging). He saw a dietician for 2 years. A 5-year-old has problems chewing and cannot tolerate any lumps in his food. He is having feeding therapy (Unique).

One baby has coeliac disease (a common digestive condition where a person has an adverse reaction to gluten) and two Unique children have constipation (Béna 2013; Unique).

> “Murray 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.” *Now 4 years*

> “He was breastfed till 4 months, no issues feeding.” *Now 7 years*

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, had delays 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 mastered between 6 and 18 months (at an average of 9 months) and walking is 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, which has been reported in around a third of children. This makes a child or baby feel floppy to handle and generally improves and may disappear with physiotherapy and exercises (Ching 2010; Schaaf 2012; Béna 2013; Unique).

> "We found that slinging Toby 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. Toby 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 normally. 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*

> "Murray 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*

> "Daniel 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).

> “ Toby 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 Toby 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. Toby 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. Toby 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 (intellectual) disabilities

Many, although not all, of the people described so far have needed support with their learning. Out of 21 people with a known level of learning difficulty, nine were described as having a mild level of difficulty; two had a mild to moderate learning disability; seven have a moderate learning disability; and three have severe learning disabilities. A further 18 people have an unspecified level of learning disability. A child with a 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; Unique).

A 16-year-old girl has dyslexia but normal intellectual development and is an A/B student, two further people were described as having good or excellent school results, and many others were described as having no problems (Kirov 2008; Ching 2010; Dabell 2012).

> “ Toby 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*

" Murray has a severe learning disability. He is in a special educational nursery with1:1 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*

" Daniel 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 (see Behaviour page 12).

" Toby 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 was delayed in most children but it is not known whether the delay was in line with the child's cognitive abilities (Ching 2010; Wisniowiecka-Kowalnik 2010; Schaaf 2012; Waterman 2012; Béna 2013). In one study over 80 per cent (17/21) had language delay (Béna 2013). First words emerged from 6 months to 6 years (average 2 years and 3 months) (Schaaf 2012; Unique). One child has a stutter and an adult had a stutter as a child but outgrew it and his speech has grown in confidence; one boy was non-verbal at 3 years but by 5 had single words such as Mama, Dada etc; another boy was non-verbal at 6 years but at 8 has some words and uses the picture exchange communication system (PECs) (Unique).

A 6-year-old boy had a severe language delay but otherwise normal development and no learning disabilities (Béna 2013).

Some children use sign language, PECs and/or computer-based approaches to help to communicate their needs and wants. All families recommend speech therapy; one family recommends the Hanen programme (a programme aimed at promoting language, social and literacy skills (www.hanen.org)).

There are many reasons for the 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 produces a guide to Communication which can be freely downloaded from www.rarechromo.org/familyguides/English/Communication%20guide%20FTNW.pdf).

❝ 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 3 at a push. Mainly nouns so he can name what he wants – 'Juice', 'biscuits'. He understands more than he can say. Toby uses PECS at nursery.❞ *3 years 11 months*

❝ Murray 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*

❝ Daniel 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 behavioural difficulties such as autism spectrum disorder or attention hyperactivity deficit disorder

Children with a 2p16.3 (*NRXN1*) deletion are often described as having happy, charming and social personalities. However, a significant number of children – although not all – show a similar pattern of behavioural difficulties.

There have been several large-scale studies of people with autism spectrum disorder (ASD) which have attempted to identify a genetic basis for their ASD. These studies have resulted in 29 people (out of a total number of 6,557 people included the studies) with ASD being diagnosed with an *NRXN1* deletion (Szatmari 2007; Marshall 2008; Bucan 2009; Glessner 2009; Wisniowiecka-Kowalnik 2010; Sanders 2011; Hedges 2012; Prasad 2012; Walker and Scherer 2013). ASD was also reported in 10 out of 17 people with a 2p16.3 (*NRXN1*) deletion (Schaaf 2012). ASD is a condition that affects social interaction, communication, interests and behaviour. It has been suggested that around two thirds of people with an *NRXN1* deletion have a diagnosis of ASD or show autistic traits. 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.

Three 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).

Attention deficit hyperactivity disorder (ADHD), hyperactivity or attention problems have also been reported (Ching 2010; Dabell 2012; Schaaf 2012; Unique). Poor concentration and fidgety behaviour seems to be an issue for quite a few children (Ching 2010; Unique).

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

> ❝ 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. Toby 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 has no issues with being mucky or wet! 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*

" Murray 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 normally 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*

" Daniel 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

There have also been several large-scale studies of people with schizophrenia which have resulted in several (31/18,704) people with schizophrenia being diagnosed with an *NRXN1* deletion (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). 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 these people with an *NRXN1* deletion has been reported between 14 and 37 years (the average age of onset is 24 years). Schizophrenia can be treated using a combination of medical treatments such as antipsychotic medicines, and psychological interventions such as cognitive behavioural therapy.

Five people in a study of 501 people with Alzheimer's disease (AD) were diagnosed with a *NRXN1* deletion (Swaminathan 2011). 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.

Sleep

Sleep problems do not seem to be common in children with a 2p16.3 (*NRXN1*) deletion. One child in the medical literature and one Unique member have been reported to have sleep disturbance (Béna 2013; Unique).

Appearance

Facial appearance

Children with 2p16.3 (*NRXN1*) deletions may have subtle unusual facial features.

Children may have a small head (microcephaly) or a large head. Geneticists trained to note unusual features may find features that are unusual but there do not seem to be any consistent specific features associated with this deletion (Béna 2013; 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); abnormal thumb; uneven finger and toe lengths; bent little fingers (5th finger camptodactyly); tapering fingers; brachydactyly (short fingers and/or toes); clubfoot; curved second toes; high foot arches. Overall, the pattern is of variable minor hand and feet anomalies (Ching 2010; Soysal 2011; Waterman 2012; Béna 2013; Unique).

Health matters

Seizures

Children with 2p16.3 (*NRXN1*) deletions have an increased risk of seizures

There have been two large-scale studies of people with epilepsy which have attempted to identify a genetic basis for their seizures. These have identified several people (6/1816) with epilepsy who carry an *NRXN1* deletion (Møller 2013; Nicoll 2013). Other studies have noted around 50 per cent of those with a 2p16.3 (*NRXN1*) deletion 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 half of those at Unique and only one child's seizures are not fully controlled with medication (Rujescu 2009; Ching 2010; Duong 2012; Schaaf 2012; Dabell 2013; Unique).

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

Joint laxity

Joint laxity (looseness or instability of the joint, also called hypermobility or double jointedness) has been reported in some people (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 (Béna 2013).

Eyesight

Eyesight problems have been very rarely reported in those people with a 2p16.3 (*NRXN1*) deletion. But the child on p11/cover wears glasses

Hearing

Generally speaking children have normal hearing. Two people have been reported with a hearing loss (Dabell 2012; Schaaf 2012). One child has hyperacusis (over-sensitivity to certain frequency and volume ranges of sound) (Béna 2013). Young children sometimes have the fluctuating temporary hearing loss caused by a build-up of fluid behind the eardrum (glue ear) but they 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).

Heart

Cardiac problems have rarely been reported. Four children were reported with holes in the heart which either closed spontaneously or were corrected surgically (Ching 2010; Schaaf 2012; Unique).

Other

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 (curvature of the spine) in two people (Soysal 2011; Schaaf 2012); anomalies in the cervical vertebra (neck) (Ching 2010; Unique); hip dysplasia (underdevelopment of the hip) (Ching 2010); a brain anomaly (Béna 2013); 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).

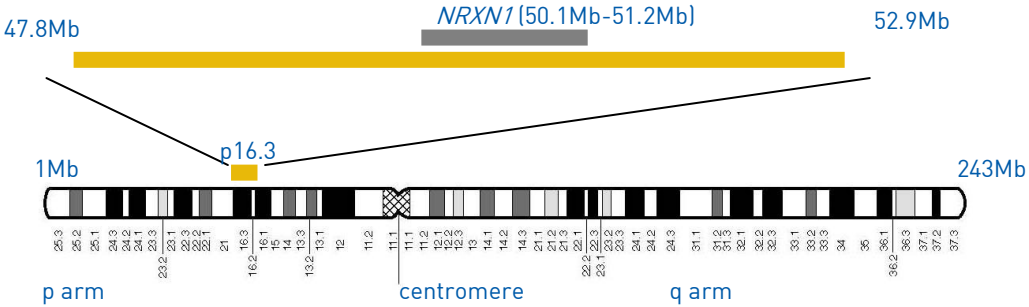
Adults with a 2p16.3 (*NRXN1*) deletion

A mixed picture

Several adults have been briefly described after their child was diagnosed. Most were unaffected by the deletion and had normal development. At least one parent is educated to degree level. 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 disabilities and short stature. A 56-year-old man with a severe learning disability lives in a group home (Dabell 2012; Béna 2013; Unique).

Research involving 2p16.3 and *NRXN1*

The microdeletion involving 2p16.3 can be as big as 5.5Mb. However, recently quite a few people who have either very small deletions which contain only the *NRXN1* gene or a single base pair change (mutation) within the *NRXN1* gene itself have been described in the medical literature. These people all 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; see page 4 for more details). Your child's report may refer to a different human genome build. Please contact Unique or your genetic specialist for any help with understanding the report.

Neurexins are a group of proteins involved in nerve cells (the building blocks of the nervous system). The nervous system controls everything a person does, including breathing, walking, thinking, and feeling. This system is made up of the brain, spinal cord, and all the nerves of the body. There are three neurexin genes (*NRXN1*, *NRXN2* and *NRXN3*). *NRXN1* located on 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*

It is thought that the loss (or partial loss or disruption) of one copy of 2p16.3 or *NRXN1* makes someone more susceptible to a learning disability, developmental delay and other features described in this guide. However, five people (one sibling pair and three unrelated people) who have lost ***both*** copies of *NRXN1* have been described in the medical literature, all of whom have a 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).

When both copies of *NRXN1* are mutated 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).

How did this happen?

In some cases the 2p16.3 or *NRXN1* deletion was inherited from a parent. However, in others the deletion has occurred out of the blue for no obvious reason. The genetic term for this is *de novo* (dn) and a blood test shows that both parents have normal chromosomes. *De novo* 2p16.3 (*NRXN1*) deletions are caused by a mistake that is thought to occur when the parents' sperm or egg cells are formed or in the very earliest days after fertilisation.

What is certain is that as a parent there is nothing you 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.

Can it happen again?

Where both parents have normal chromosomes, 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 normal 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 are appear normal when their blood is tested can have more than one child with the deletion.

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 in each pregnancy.

If they wish, parents should have the opportunity to meet a genetic counsellor to discuss the specific recurrence risks and options for prenatal and preimplantation genetic diagnosis (PGD). PGD requires the use of *in vitro* fertilisation and embryo biopsy, and only healthy 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 of these tests are available in all parts of the world.

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 normal. In each pregnancy, someone with the deletion is likely to have a 50 per cent risk 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 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!**"**

Notes

Inform Network Support

Rare Chromosome Disorder Support Group,
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Join Unique for family links, information and support.

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