How common is the 2p16.3 (*NRXN1*) 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.

Why 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 "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 (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.

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!"

Inform Network Support

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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. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This information guide was compiled by Unique (CA) using information from the comprehensive Unique information guide to 2p16.3 (*NRXN1*) deletions (2024) and reviewed by Dr Christian Schaaf, Director and Chairman, Institute of Human Genetics, Heidelberg University Hospital, Germany.

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Understanding Chromosome & Gene Disorders

2p16.3 (*NRXN1*) deletions

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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.

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 featured 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.

What is the outlook?

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.

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.

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.

Neurexin 1 (*NRXN1*)

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.

Most common features

Every person with a 2p16.3 (*NRXN1*) deletion is unique. However, several common features have emerged:

- Children are likely to need support with learning
- Speech and language delay
- Behaviours and diagnoses such as an autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) disorder
- Seizures
- Most children are otherwise generally healthy

Development

Gross and fine motor skills

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. One of the causes of the delay 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.

Hypotonia can also affect fine motor skills and children may take longer to reach for and grab toys, hold a bottle or cup, self-feed, dress themselves, and hold a pen to write or draw. Toilet training may also be affected.

Learning

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. Many children with an *NRXN1* deletion have no learning disability and encounter no problems in school.

Speech and language

Speech and language development is delayed in many, but not all, children with a 2p16.3 (*NRXN1*) deletion and some children are non-verbal. It is possible for speech and language delay to occur in children who have otherwise typical development and no learning disability. Children may find sign language or picture exchange communication systems (PECs) beneficial to help communicate their needs and wants. Unique families recommend speech therapy.

Behaviour

Children with a 2p16.3 (*NRXN1*) deletion are often described as having a happy, charming and social personality.

Some children have diagnoses such as an autism spectrum disorder (ASD) or attention hyperactivity deficit disorder (ADHD). Some children have been reported with sensory integration (processing) disorder (SPD).

A few children have been described as having no sense of danger or demonstrating self-injurious behaviour and several children and adults have been described as having anxiety. Quite a few children have poor concentration and fidgety behaviour.

Late-onset conditions

Having an *NRXN1* deletion may increase the chance of developing the conditions Alzheimer Disease (AD) and schizophrenia. 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. Schizophrenia can be treated using a combination of medical treatments, such as antipsychotic medicines, and psychological interventions, such as cognitive behavioural therapy.

Feeding & growth

Feeding and growth are often not affected in children with a 2p16.3 (*NRXN1*) deletion, although a few have been reported to have faltering growth or poor weight gain. A few babies have been reported to have feeding difficulties, which may be due to hypotonia. The floppiness can also affect their food pipe and contribute to some babies having gastro-oesophageal reflux. Babies with this condition may need and benefit from interventions such as a fundoplication, a nasogastric tube or a gastric tube. A few Unique children have features of an oral sensory issue, such as food colour aversion and gagging. Several have chronic constipation.

Medical concerns

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. 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.

Other conditions

Children may have a small head (microcephaly) or a large head (macrocephaly). Minor anomalies of the hands and feet; eyes and vision; hearing; joints; heart; and genitals have been reported rarely.