How common is *NONO*-associated X-linked ID syndrome?

NONO-associated X-linked ID syndrome is very rare. Currently (March 2021) 11 children with this diagnosis have been reported in the medical literature. It is expected that more children will be diagnosed with this condition as awareness increases and genetic testing becomes more routine. It is important to know that the most severely affected children are likely to be the first identified so initial findings may not represent the possible spectrum of symptom severity.

Why did this happen?

When children are conceived, the genetic material is copied in the egg and sperm that make a new child. The biological copying method is not perfect, and 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 any lifestyle, dietary or environmental factors. No one is to blame and nobody is at fault. Such changes happen to everyone but it's only when a change affects an important gene that health and/or development are affected.

In most children diagnosed with *NONO*-associated X-linked ID syndrome so far, the change in the *NONO* gene occurred by chance in that child (this is known as *de novo*) and was not found in their parents. However, a few children are known to have inherited a pathogenic variant of the *NONO* gene from an unaffected or mildly affected mother.

Can it happen again?

The risk of having another child affected by a rare gene disorder depends on the genetic code of the parents. If the change in the *NONO* gene has been shown to be *de novo*, that means neither parent was found to carry it, the chance of having another child with *NONO*-associated X-linked ID syndrome is low (1% to 2%). The reason there is still a small chance is due to something called germline mosaicism, which is where the gene variant can be found in a few eggs or sperm, but is not found in the rest of the body's cells.

If a mother is found to carry the genetic variant, the chances of having another child with the NONO variant is 50% for each pregnancy. A clinical geneticist or genetic counsellor can give you specific advice for your family.

Can it be cured?

NONO-associated X-linked ID syndrome cannot be cured at the present time however, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

Families say .....

" We have been looking for an answer for 10 years, the doctors had no idea if it was going to be a genetic change - NONO. It was only when little brother came into the world, and it turned out he also had LVNC. After that, our journey started to a connection between the two boys and me. We still know VERY little, as the doctors have not seen it before. "

" The biggest thing for us was knowing we weren't alone anymore I suppose, 16 years was a long time not knowing our son was the way he was, it has explained lots about his behaviour. "

" Finding out our son had NONO syndrome at the age of 14, and finding families with children just like ours, made me feel so much better - I could talk to families and not feel alone. "

" A list of things to look out for but not necessarily expect would be very helpful- as we know not everyone affected is affected the same. "

Inform Network Support

Rare Chromosome Disorder Support Group,
The Stables, Station Road West,
Oxted, Surrey. RH8 9EE. UK.
Tel +44(0)1883 723356
info@rarechromo.org
www.rarechromo.org

Facebook groups and other links:

NONO Gene Mutation:
www.facebook.com/groups/1597987633834443
Mighty Max NONO gene mutation:
www.facebook.com/groups/1569014886645106

Join *Unique* for family links, information and support.

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org/donate Please help us to help you!

Understanding Chromosome & Gene Disorders

NONO-associated X-linked ID syndrome

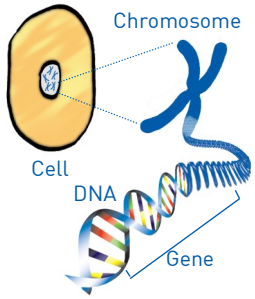
rarechromo.org

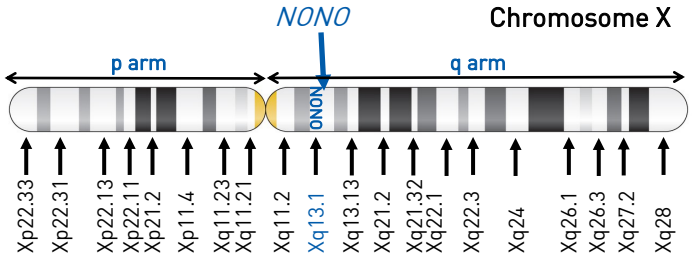
What is *NONO*-associated X-linked ID syndrome?

NONO-associated X-linked ID (intellectual disability) syndrome is a rare genetic condition that causes developmental delay and can affect a child's learning abilities and behaviour. As is common with genetic conditions, each person is affected differently but males are expected to be more severely affected than females. Children with *NONO*-associated X-linked ID syndrome can experience medical concerns associated with the heart, the gastrointestinal system and the hormonal system.

What causes *NONO*-associated X-linked ID?

NONO-associated X-linked ID syndrome is caused by specific changes (known as pathogenic variants) to, or a deletion of, a gene called *NONO* (also known as Non-POU Domain Containing Octamer Binding Protein). The *NONO* gene is located on the X chromosome, this is why the syndrome is called X-linked. It is positioned in Xq13.1 (meaning in the 'q' arm in a band called 13.1 as shown in the image below)





Females usually have two X chromosomes, so have two copies of the *NONO* gene. Males have an X and a Y chromosome, so only have one copy of the *NONO* gene. If the gene is altered in a way that affects its function, it is more likely that a boy will show symptoms since he does not have a second copy of the gene. Since females do have a second copy of *NONO*, girls are less likely to be affected. However, the situation can be complicated by a natural process called X-inactivation, where one X chromosome is almost completely 'switched off'.

The *NONO* gene sequence is used to make the NONO protein. This protein is part of an important group of proteins that control the activity of other genes. NONO has a specific pattern of activity in different parts of the brain, especially during development, so changes to its function may cause neurological difficulties such as those associated with learning and behaviour.

NONO-associated X-linked ID syndrome features

Children have:

- Developmental delay and intellectual disability (ID)
- Autistic spectrum disorder (ASD)

Other possible features include:

- Heart anomalies
- Weak muscle tone (hypotonia) & joint hypermobility
- Gastrointestinal symptoms
- Genitourinary anomalies
- Seizures
- Brain anomalies
- Eye anomaly
- Hormone deficiency
- Skeletal anomalies

Medical concerns

Heart Anomalies

Heart anomalies have been reported affecting the size and structure of the heart muscle and valves. Seven out of eight children tested have been found to have a thick and spongy heart muscle [left ventricle non-compaction (LVNC)], one child has an Ebstein's anomaly (affecting a heart valve) and one child has an underdeveloped (hypoplastic) left heart.

Hypotonia

All children reported so far have been found to have weak muscle tone (hypotonia) and joint hypermobility.

Genitourinary Anomalies

Anomalies of the genitalia have been reported such as hypospadias (where the opening of the penis is found on the underside) and undescended testes. Hormone deficiency can affect development during puberty.

Seizures

Some children with *NONO*-associated X-linked ID syndrome experience seizures or have had a seizure but there is currently very little information regarding seizure activity.

Brain anomaly

Some children with *NONO*-associated X-linked ID syndrome have had a brain MRI. Thickening of the corpus callosum, mild Arnold Chiari malformation and pituitary gland anomalies (which can lead to hormone deficiency) have been reported.

Eye anomaly

A strabismus (squint) has been reported in children with *NONO*-associated X-linked ID syndrome.

Skeletal anomalies

Many children reported so far have developed a curvature of the spine (kyphoscoliosis). Funnel chest (pectus excavatum) has also been reported.

Head circumference

Many children with *NONO*-associated X-linked ID syndrome have a larger than usual head circumference.

Development

Physical Development

Developmental delay of motor function, for example walking, has been reported in all children diagnosed with *NONO*-associated X-linked ID syndrome so far (2021).

Intellectual Development and Learning

Children with *NONO*-associated X-linked ID syndrome usually have some level of intellectual disability.

Speech and language

Some form of language developmental delay has been reported in all of the children diagnosed to date (2021), some children may not learn to speak.

Behaviour

Some children with *NONO*-associated X-linked ID syndrome have been diagnosed with a neurodevelopmental disorder or difficulty including ASD (autism spectrum disorder) and sleep difficulty. Routine and predictability can be very helpful for these children.

Feeding

Feeding has been problematic for all children with NONO-associated X-linked ID syndrome. Many of the children reported so far have had feeding difficulties, with severe gastro-esophageal reflux, cyclical vomiting and constipation. All children known to date have required nasogastric (NG) tube feeding (when a tube is passed through the nostril directly to the stomach to administer feeds). One mother reported that her child tolerates being fed very well with blended or pureed food.

"he likes eating and he is happy and well behaved at mealtimes."

"He has made amazing progress and is now orally fed but requires a PEG to top up fluids and for medication."

Weight

Children with *NONO*-associated X-linked ID syndrome assessed so far are generally described as having slim stature.

Height

Some children with *NONO*-associated X-linked ID syndrome reported so far, have short stature. In some this has been associated with hormone deficiencies.

Management recommendations

Children with NONO-associated X-linked ID syndrome should be under the care of a multidisciplinary team including a geneticist, paediatrician and the Community Paediatric team with neuro-developmental paediatrician, physiotherapy, occupational therapy and speech and language therapy. Imaging of the heart is recommended. Children should be referred to an Ophthalmologist (Eye Doctor) for assessment.