Understanding Chromosome & Gene Disorders

HNRNPH2-Related Neurodevelopmental Disorder

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What is *HNRNPH2*-Related Neurodevelopmental Disorder?

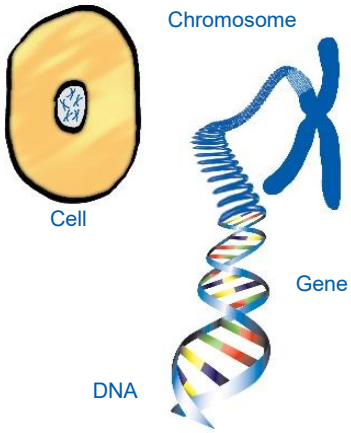
HNRNPH2-related neurodevelopmental disorder (*HNRNPH2*-NDD for short), also referred to as Bain syndrome and Bain type syndromic intellectual disability, is a rare genetic condition associated with developmental delay, intellectual disability, autistic spectrum disorder, reduced muscle tone, and seizures. As is common with genetic conditions, each person is affected differently.

HNRNPH2-NDD is caused by a change (variant) in the *HNRNPH2* gene.

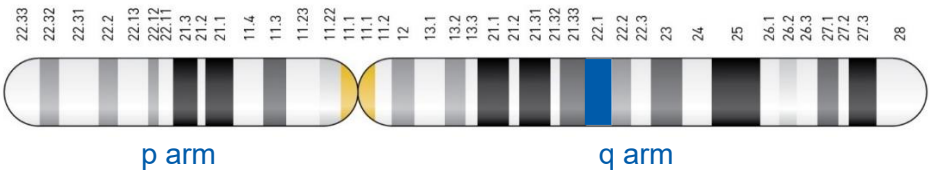
What causes *HNRNPH2*-Related Neurodevelopmental Disorder?

Genes are instructions which have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies.

HNRNPH2-NDD is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called *HNRNPH2*, which is an abbreviation of the gene's full name, heterogeneous nuclear ribonucleoprotein H2. The *HNRNPH2* gene is located in the long 'q' arm of chromosome X in a region called Xq22.1 as shown as a blue band in the image below.



Chromosome X



Females usually have two X chromosomes and so have two copies of the *HNRNPH2* gene. Girls with a change to one copy of their *HNRNPH2* gene also have an unaffected copy of the gene on their second X chromosome that can partially compensate for the altered function of the affected gene. However, one X chromosome in each cell is 'inactivated' and the effect of X-inactivation on *HNRNPH2*-NDD in girls is not yet fully understood. (X-inactivation is a natural process that occurs in all females).

Unique publishes a separate guide on X-inactivation.

Males do not usually have two X chromosomes, instead they have one X and one Y chromosome. This means that they only have one copy of the *HNRNPH2* gene. If the gene is altered in any way, then boys do not have a second copy to compensate. This means that boys are usually more severely affected by *HNRNPH2*-NDD, but this is not always the case.

The *HNRNPH2* gene sequence is used to make a protein called the heterogeneous nuclear ribonucleoprotein H2 protein. The role of this protein in humans is not fully understood, but research in animals shows it plays an important role in the development of nerve cells (also known as neurons). Changes in *HNRNPH2* which lead to *HNRNPH2*-NDD are believed to be 'gain of function' changes (sometimes abbreviated to GOF) which alter the HNRNPH2 protein's action within the cell, which is likely to affect the development of neurons.

Genetic Report

An example result of a DNA sequencing test (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)), that can identify gene variants, is shown here for the *HNRNPH2* gene:

p.Arg212Gly (R212G): c.634 A>G in the *HNRNPH2* gene (GRCh38 NM_019597.4)

p.Arg212Gly (R212G)	signifies the change to the protein (p.): the amino acid arginine (Arg) has been replaced by the amino acid glycine (Gly) at position 212 in the sequence of amino acids that make up the protein (R is the abbreviation of Arg and G is the abbreviation of Gly)
A>G	signifies the gene sequence change; the A nucleotide has been replaced by a G nucleotide
c.634	signifies the base pair position of the change within the gene sequence
HNRNPH2 gene	signifies the gene that is affected
NM_019597.4	denotes the reference sequence used.

Unique publishes a separate guide to Interpreting genetic test results.

Common features

Most children with *HNRNPH2*-NDD have:

- Some degree of developmental delay, typically severe
- Some degree of intellectual disability, typically severe
- Altered muscle tone. In most cases reduced (hypotonia), but increased (hypertonia) is also reported
- Speech difficulties with little to no speech
- Behavioural difference, e.g. anxiety, autistic spectrum disorder (ASD) and ADHD
- Variable facial features including almond shaped eyes and small chin
- Feeding difficulties, support with a feeding tube may be required
- Joint and bone anomalies including scoliosis and hip dysplasia
- Visual problems, particularly squint
- Seizures with no particular type
- Difficulty getting to and remaining asleep
- Small head size (microcephaly)

Other possible features include:

- Hearing loss is often reported by parents
- Self-harming behaviour
- Developmental regression, sometimes associated with an illness and followed by regaining lost skills
- Gastrointestinal issues including reflux, abdominal pain and loose stools

Appearance

Certain facial features are found more often in children with *HNRNPH2*-NDD than in other children. These features may mean that you see unexpected similarities between your child and others with *HNRNPH2*-NDD. The most common characteristic features include almond shaped eyes, short groove between the nose and the upper lip (philtrum), small sides of the nose around the nostrils (alae nasi), full lower lip and small chin.

Development

Gross and fine motor skills

Developmental delay has been reported in all children with *HNRNPH2*-NDD so far (2024). The degree of delay is typically severe. Developmental "milestones", including rolling, sitting, walking, playing with toys, using cutlery, using zips and buttons, and toilet training, are often delayed, although there is a range of eventual ability. Low muscle tone (hypotonia) is common and may affect mobility. High muscle tone (hypertonia) has also been described, but is less common, and may also affect mobility. Some children may have an unusual gait when walking because of stiffness, or balance issues (known as ataxia). For some children, independent walking may not be achieved. Many children benefit from early support by physiotherapy (PT) and occupational therapy (OT).

Unique publishes separate guides to Therapies and Toilet training and continence.

Intellectual development and learning

All children with *HNRNPH2*-NDD reported so far (2024) have intellectual disability (ID) or learning difficulties. ID varies but is usually in the severe range and specialised schooling is usually required. Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended.

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

Speech and language

Children with *HNRNPH2*-NDD typically experience speech and language delay, and many are non- or minimally verbal. Many children find it difficult to co-ordinate movement of their lips, jaw and tongue to make the right sounds (this is known as apraxia of speech). Those who do develop speech may achieve single words and short phrases.

An assessment by a speech therapist should be able to identify a child's specific difficulties, allowing regular therapy sessions tailored to each child's specific areas of need. Where individuals have no speech or very few words, Augmentative and Alternative Communication (AAC) methods, including pointing, pictograms, gestures, facial expression and simplified sign language and high-tech communication systems (aided communication) may aid communication.

Unique publishes a separate guide to Communication.

❝ I would say that the majority of our children have a passion for music/singing. Music is our child's life as I believe many others will agree. We had invaluable support from the portage service when she was about one year old. I cannot recommend this enough. ❞

❝ Our daughter also lives for eye contact. She will seek eyes out and hold on to that gaze for as long as you are willing. She also loves to touch people's hands. Her very own way of communicating. ❞

Feeding and gastrointestinal problems

Feeding issues in the new-born period for babies with *HNRNPH2*-NDD are common. Low muscle tone may contribute to difficulties with swallowing and some babies will suck weakly and may need high energy milks to encourage weight gain.

Some babies also suffer from gastro-oesophageal reflux (GERD/GORD) (in which feeds return readily up the food passage), which may require treatment, including careful positioning for feeds, medication or nutritional supplements. For some children, insertion of a nasogastric tube (NGT) or percutaneous endoscopic gastrostomy tube (PEG/G-tube) is required to either aid feeding or prevent reflux. Other issues that have been reported include aspiration (where fluid, food or saliva enters the airway or lungs).

Some children have benefited from attending a feeding clinic where an assessment can be made, and advice to help treat any eating and drinking difficulties provided.

Overeating, as well as eating things which are not considered food (pica) has occurred in some children with *HNRNPH2*-NDD.

Constipation is common among children with *HNRNPH2*-NDD and can be related to low muscle tone, little exercise, a low-bulk diet and small fluid intake, among other reasons that are not fully understood. In some cases, children with *HNRNPH2*-NDD can have loose stools.

It is important to discuss the possible causes of feeding difficulties and gastrointestinal problems with a health visitor or doctor, who may recommend diet adaptation or treatment such as giving stool softeners or laxatives.

Unique publishes a separate guide to Feeding.

❝ Due to hypotonia, swallowing can be difficult. We had many serious choking incidents when our daughter was between one and five years old. She can also suffer from excessive saliva which will sometimes require suction. She struggled to feed for a long time. She was supplemented by a nasal gastric tube and progressed to a peg. She still has this for fluids and medicines. ❞

Growth and stature

Growth is likely to be affected due to feeding difficulties. Children with *HNRNPH2*-NDD are therefore likely to be shorter than expected but remain within normal ranges when feeding is optimised. Some children with *HNRNPH2*-NDD have a smaller head than expected, though this is not usually present from birth, and becomes apparent as they grow with their head growth not keeping up relatively with the growth of the rest of the body (this is known as acquired microcephaly).

Behaviour

Children with *HNRNPH2*-NDD typically tend to have behaviour in keeping with their overall degree of developmental delay. Some children have an autism spectrum disorder (ASD) diagnosis, attention deficit hyperactivity disorder (ADHD) or have been diagnosed with anxiety. Other behaviours including actions that may harm themselves have also been reported. Many children also have sleep problems which can have a significant impact on behaviour. Children usually benefit from consistent routines, boundaries, rewards and other behaviour management techniques. Efforts to take into account and introduce strategies to tackle communication and other difficulties can also be beneficial.

Unique publishes separate guides to Challenging Behaviour and Sleep.

❝ Our children have a number of strengths. Very emotionally attuned, huge smiles/happy demeanour, love for music and dance, love for people and connection with others, ability to progress and develop, their own unique personalities. ❞

Puberty

Children with *HNRNPH2*-NDD tend to go through puberty at the normal ages (8 to 13 years in girls, 9 to 14 years in boys), though both early and delayed puberty have been seen in children with this genetic condition.

Unique publishes a separate guide to Puberty.

Adults with *HNRNPH2*-NDD

The majority of people identified with HNRNPH2-related neurodevelopmental disorder to date (2024) are children and the information on HNRNPH2-NDD in adulthood is limited, though there are some cases. The oldest living individual known to have HNRNPH2-related neurodevelopmental disorder was described at 38 years of age. There is no evidence that the condition worsens in early adulthood, or that life expectancy is reduced, but more research is needed.

Medical concerns

The following medical concerns have been found in children with *HNRNPH2*-NDD. They are not found in all children so not all children with *HNRNPH2*-NDD will be affected.

Heart conditions

A heart condition has been found in a few people reported so far (2024) with *HNRNPH2*-NDD which can be present at birth. These heart conditions were mild and did not require surgery. In children for whom heart problems are suspected, these can be diagnosed using tests like an electrocardiogram (ECG) (recording the electrical activity of the heart), echocardiogram (ultrasound scan of the heart), or chest X-ray. The type of heart condition is variable with no single predominant condition.

Brain anomalies

When scanned, the brains of children with *HNRNPH2*-NDD are typically normal in appearance. A few children have been found to have subtle changes in their brain, including reduced volume of the cerebellum and thinning or altered position of the corpus callosum.

“ Our daughter’s MRI showed a lack of white matter in the brain. Her ECGs showed a typical wave for a child with neurodevelopmental delay. ”

Seizures

Many children with *HNRNPH2*-NDD experience seizures. The most common seizure type is staring episodes (also known as absence seizures), but many other types of seizure are also seen with the condition. Children with *HNRNPH2*-NDD with seizures may or may not have abnormal findings of an electroencephalogram (EEG).

Seizures can cause a lot of worry for families and can be frightening to observe, but they can self-resolve or resolve with medical treatment. Affected children tend to respond well to levetiracetam and sodium valproate for seizure control.

When a child has a seizure for the first time, it is important to remove nearby hazards so they can't hurt themselves and contact a medical professional. It may also be of use to record unusual behaviours such as staring episodes to help with the diagnosis of absence seizures.

Febrile seizures (a seizure as a direct result of a fever which is most often caused by a viral illness) are common in young children, but more common in children with *HNRNPH2*-NDD. Having a febrile seizure does not necessarily mean that a child will go on to have other types of seizures.

❝ I would say many of our children have fits that are not necessarily text book. They may start as focal and dip in and out of tonic-clonics. Our daughter has facial quivers and produces lots of saliva when having an episode. She had a huge tonic-clonic once but kept clicking her finger throughout the whole episode! ❞

❝ Many of our children have epilepsy that is controlled with 'Levetiracetam'. ❞

■ Eyes and eyesight

The majority of children with *HNRNPH2*-NDD have an eye or vision anomaly. A wide range of conditions have been reported and an individual may have more than one vision or eye-related concern. The most common condition is a squint (also known as a strabismus). Shortsightedness (myopia) and poor vision are not uncommon.

❝ Many of our children are reported to have cortical vision impairment (CVI). It's incredibly hard to test for this due to communication difficulties. But knowing this is a high probability with our children enables us to be on the lookout continually and explain to specialists at appointments. ❞

■ Hearing

Hearing impairment in children with *HNRNPH2*-NDD is reported by some parents. No particular type of hearing loss is recognised, however. Hearing tests at birth may give a clear response. Many types of hearing loss can be managed by using hearing aids.

Some children experience recurrent ear infections and “glue ear”, where fluid builds up behind the ear drum. Glue ear is a type of conductive hearing loss and is typically treated by inserting aeration tubes (grommets) into the eardrum.

Unique publishes a separate guide to Hearing.

■ Spine

Many babies with *HNRNPH2*-NDD are born with or develop a spinal curvature, either a sideways curve of the spine (scoliosis), a rounding of the upper back (kyphosis) or kyphoscoliosis (a combination of kyphosis and scoliosis). The curvature can be treated with physiotherapy and exercises, or a support brace or surgery may be needed.

■ Joint anomalies

Joint anomalies are a known feature of *HNRNPH2*-NDD. These include joint pain and stiffness. Contractures may also occur (especially in those with increased muscle tone) which can be painful and limit movement. Physiotherapy and occupational therapy support with regular movements may aid this.

Hip dysplasia (impaired development of the hip socket) is also seen with this condition. This is typically treated with a special harness (Pavlik harness) if caught early.

How common is *HNRNPH2*-NDD?

HNRNPH2-NDD is extremely rare. Currently (2024) just under 50 individuals with *HNRNPH2*-NDD have been reported but over 150 individuals with an *HNRNPH2* gene variant have been identified. It is expected that more people with this condition have been diagnosed but not reported in the medical literature and more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

Why did this happen?

When children are conceived, their parents’ genetic material (DNA) is copied in the egg and sperm that makes a new child. The biological copying method is not perfect, and random changes occur in the genetic code of all children, that are not seen in the DNA of their parents. This happens naturally and is not due to the parents’ diet, environment or lifestyle. Most of these DNA changes have no obvious effect. But in rare

instances these random DNA changes can lead to health issues or affect development. When such a random change disrupts the function of the *HNRNPH2* gene in a specific way then a child will have *HNRNPH2*-NDD.

In almost all people identified so far (2024) with *HNRNPH2*-NDD, the genetic change was a random (or "*de novo*") change, meaning the change occurred for the first time in that family in the affected individual. Very rarely, one parent may have the same change (or variant) in some of their cells and pass it on to their child (this is known as mosaicism). However, it is important to recognize that 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?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. If the genetic alteration is thought to be *de novo*, which means neither parent was found to have the same *HNRNPH2* gene change as their child then the chance of having another child with *HNRNPH2*-NDD is usually less than 1%.

One reason why there is some residual chance of recurrence is due to the rare phenomenon known as germline mosaicism. This is when a parent carries a genetic change, but it is limited to some of their egg or sperm cells. The genetic change would not, therefore, be detected in the parents' blood tests.
There is also a very rare chance that a mother may unknowingly carry an HNRNPH2 variant if she has a significantly skewed X-inactivation pattern, where the X chromosome with the variant is inactivated in most of her cells. This is known to have occurred in at least one family.

Unique publishes a short general guide to mosaicism.

A clinical geneticist or genetic counsellor can provide specific advice for each family about the chance of having further children with *HNRNPH2*-NDD. *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.

Can *HNRNPH2*-NDD be cured?

There is no cure for *HNRNPH2*-NDD since the effects of the genetic change took place during a baby's formation and development. However,

knowing the diagnosis means that appropriate monitoring and interventions can be put in place.

Management recommendations

Children with *HNRNPH2*-NDD should be under the care of a multidisciplinary team. The team should include a geneticist and paediatrician or paediatric neurologist who can oversee care so that development and behaviour can be monitored, and the best help given in the form of physiotherapy, occupational therapy, speech therapy and, if needed, behavioural therapy. Individuals may have evaluations with ophthalmology, audiology, gastroenterology and cardiology where appropriate.

Families say …

❝ When your child is diagnosed with a rare genetic condition it throws up all kinds of painful emotions. Ultimately you want to give them the best and that can feel like a big responsibility. It takes time to process and learn everything, be kind to yourself and know that Unique and The Yellow Brick Road community will support you through this unexpected journey. ❞

❝ Receiving our daughter's diagnosis was a relief in a way. Being able to join a group of other people who have children with the same condition has given reassurance and invaluable guidance as to what symptoms may look like or how we can help them. With a huge list of symptoms to digest, it's daunting and terrifying! Knowing that others are successfully living this path too is imperative to me at times.

Despite all of our daughter's challenges, she really is a tonic for the world. She brings smiles and pure love to anyone she meets. Our days may not be lived how we imagined but we really thank our lucky stars for the joy she brings to our life every single day.

Yellow brick Road is a very active community run by passionate parents/scientists who strive to spread the word about HNRNPH2 and continually push for more knowledge and future medicines. ❞

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members.

Inform Network Support

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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!

Websites and Facebook groups:
Yellow Brick Road Project
https://yellowbrickroadproject.org
https://www.facebook.com/HNRNPH2

This information 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. This guide was written by Dr Edward Steel, Clinical genetics, London North West University Healthcare NHS Trust.

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