Unique

Understanding Chromosome & Gene Disorders

# *GRIN2B*-related neurodevelopmental disorder (*GRIN2B*-related syndrome)

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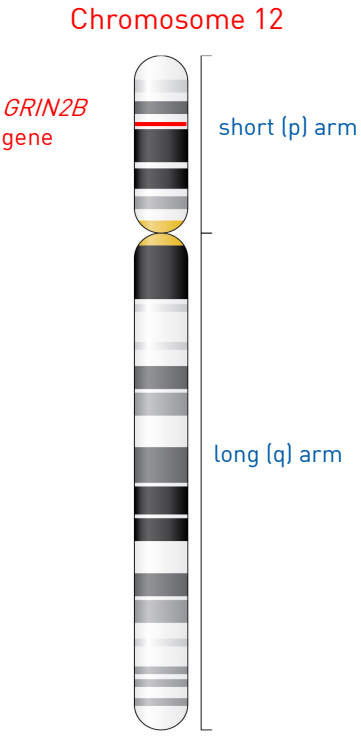
## What is *GRIN2B*-related neurodevelopmental disorder and what causes it?

*GRIN2B*-related neurodevelopmental disorder is a condition that is associated with some degree of developmental delay and learning (intellectual) disability. Some people with this condition also have other features, including low muscle tone (hypotonia), seizures and behavioural differences. *GRIN2B* is one of a family of seven GRIN genes that play an important role in the transmission of signals in the brain. This is why developmental delay/learning disability is an important feature of *GRIN2B*-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 in our cells, the building blocks of our bodies.

The *GRIN2B* gene is found in the short (p) arm of chromosome 12 in a band called 12p13.1.

People have two copies of chromosome 12, and so two copies of the *GRIN2B* gene. The syndrome occurs when one of the two copies of the *GRIN2B* gene does not function as expected. This can be caused by specific changes in the gene (known as pathogenic variants) or by the loss of the whole (or part) of one copy of the gene (known as a deletion). The severity of intellectual disability and other features observed depends to a certain extent on the type of pathogenic variant in the *GRIN2B* gene that has detected in that individual.

*GRIN2B*-related neurodevelopmental disorder was first described in 2010.

More information on the genetic causes of *GRIN2B*-related neurodevelopmental disorder can be found on the GRIN2B foundation website (see page 10 for details).

### Most children with *GRIN2B*-related neurodevelopmental disorder have:

- developmental delay and/or learning (intellectual) disability

### They may also have:

- seizures
- low muscle tone (hypotonia)
- increased muscle tone or stiffness (spasticity)
- a movement disorder
- a small head circumference (microcephaly)
- eyesight and vision anomalies
- behaviour differences, including autism spectrum disorder (ASD) or autistic features
- brain anomalies (very rarely)

## How many people have this condition?

More than 100 children with *GRIN2B*-related neurodevelopmental disorder have been described in the medical literature or gene-specific databases (2022) (although more children will have received a diagnosis but not been reported). With the increasing use of the latest 'gene sequencing' technology, it is expected that many more people will be diagnosed with this condition over the coming years. In recent years, a number of Support/Facebook Groups, including the *GRIN2B* Foundation, have been set up. See page 10 for details.

# Medical concerns

## Seizures and brain anomalies

Approximately one third to a half of children with *GRIN2B*-related neurodevelopmental disorder experience seizures. The number of seizures can vary from multiple episodes per day to a few seizures per year; some have become seizure-free later in life.

Very few children have a severe form of epilepsy which can be associated with a stagnation or even decline in their development (West syndrome or Lennox-Gastaut syndrome).

A minority of individuals with severe to profound developmental delay, cerebral palsy and seizures exhibit a brain anomaly including a malformation of cortical development that can be detected by magnetic resonance imaging (MRI) scan.

## Low muscle tone (hypotonia)

Many children with *GRIN2B*-related neurodevelopmental disorder have low muscle tone (hypotonia). This can result in a delay in reaching certain developmental milestones such as rolling, sitting, crawling and walking. It may also contribute to the feeding difficulties seen in some children.

## Eyesight and eyes

Some children have an eye anomaly or problems with vision, which are quite varied. These include long-sightedness (hypermetropia) or short-sightedness (myopia), a squint (strabismus) and involuntary eye movements (nystagmus). Many of these eyesight differences can be corrected with surgery (such as strabismus) or glasses (such as long- or short-sightedness).

A small minority of children have cortical/cerebral visual impairment (CVI). This is where a difference in the development of the parts of the brain that are responsible for processing vision mean the brain can't consistently interpret and understand what the eyes see, leading to problems with vision. People may therefore have a CVI despite there being no problems with their eyes.

# Development and behaviour

## Growth

Growth in children with *GRIN2B*-related syndrome mostly appears to be unaffected. A minority of children have a small head circumference (microcephaly), usually associated with more severe learning disability.

## Feeding

Feeding issues and/or constipation have been reported in some babies and children. Low muscle tone may make it difficult to suck, chew and swallow, which can lead to issues with feeding. Occasionally, a child may require a period of feeding via a nasogastric tube (an NG tube), where food is delivered directly to the child's stomach via a tube inserted through their nose. A minority of babies

readily bring feeds back up (gastro-oesophageal reflux) and may need careful positioning while feeding and sleeping. Some children continue to have difficulties with solid food and may choke or gag easily. A feeding or speech therapist can help to find ways to feed children with feeding difficulties.

### Families say ...

“ Acid reflux from 9 months until about 2½, but was eating normal table food with no problem by the age of 2. ”

“ She was very underweight as a baby until she had an NG tube [feeding tube through the nose]. She vomited as a baby up to 8 times a day until she had a Nissen fundoplication [surgery to tighten the valve between the food passage and the stomach]. Today she takes nil by mouth as she has no interest in food or drink. She is gastrostomy fed [direct to the stomach], and perhaps that is why she is big for her age. ” - 8 years

## Sitting, moving & walking

Many children with *GRIN2B*-related neurodevelopmental disorder show a delay in reaching developmental milestones. Some children do learn to sit and walk independently, but this is not possible for all and some may benefit from using mobility aids, such as a walking frame or wheelchair. A very small minority of children showed signs of developmental regression, where they temporarily lost some of their abilities in sitting, crawling and walking. Some children exhibit involuntary movements and spasms in parts of their bodies. These movements may be sudden and repetitive.

### Families say ...

“ She could sit on her own at 13 months, and take a few steps at a time at 26 months, walking distances around 27 months. ”

“ She couldn't hold her head up until she was 3 years old at least. She cannot sit up or walk and needs a wheelchair to get around. ” - 8 years

## Speech & Learning

Children with *GRIN2B*-related neurodevelopmental disorder show some degree of intellectual (learning) disability. The degree can range from mild to severe. Speech and communication is one of the most commonly affected areas of development. Children are often non-verbal or use only single meaningful words. Some go on to communicate in short phrases or sentences. Augmentative and Alternative Communication (AAC) methods, including pointing, pictograms, gestures, simplified sign language and high-tech communication systems (aided communication) may aid communication, allowing children and adults to signal their needs and thoughts.

### Families say ...

❝ Non-verbal, but can do 3 signs and understands several others. We think she may be trying to repeat the word hi. ❞ - 3 years

❝ Likes to shout and occasionally babble a little.❞ - 8 years

❝ Laughs a lot at my voice, squeals and cries and likes to blow raspberries! ❞ - 8 years

## Behaviour

The testimony we have from *Unique* families speaks to children who are sweet, happy and friendly - sometimes overly so with strangers. Behavioural concerns are common in children with *GRIN2B*-related neurodevelopmental disorder. Some children have a diagnosis of autism spectrum disorder (ASD) or show autistic traits. Sensory processing disorder (SPD), attention deficit disorders, hyperactivity and other issues with attention or concentration may also be seen. Aggressive behaviour and sleeping problems have also been described for some.

### Families say ...

❝ Generally a happy little girl, except when she is experiencing teething pain or is frustrated. She has sensory seeking behaviors, puts everything in her mouth and likes deep pressure – massage, swinging, tight hugs. She is very curious, and loves to just wander around and explore. Like any toddler, she loves to be a troublemaker and will throw anything in her reach onto the floor. ❞ - 3 years

### Families say ...

❝ So sweet and loving in her own way. Angelic nature. Always smiling. Likes to tap a lot on her chest or other people or her toy piano or buzzer toys. LOVES sounds and any repetitive sound such as a door squeaking or a chopping sound: she sometimes goes a little mad squealing and laughing and can't calm down. She loves being in water - hydrotherapy or bath.❞ - 8 years

❝ As a baby, she cried almost continuously day and night, but today she is very sweet and friendly and adorable. She loves being with familiar people, and smiles a lot but still has periods of crying for no known reason. She loves to kick her legs and flap her arms. ❞ - 8 years

## Can this be cured?

There is no cure as the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

## Why did this happen?

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 lifestyle or anything a parent did or did not do.

There may be very rare cases where one parent has the same genetic change in *GRIN2B* as their child, but in almost all children with *GRIN2B*-related neurodevelopmental disorder, the change will have occurred out of the blue (*de novo*). A spontaneous change in the *GRIN2B* gene cannot be prevented. No environmental, dietary or lifestyle factors are known to cause any spontaneous gene change in the *GRIN2B* gene. No one is to blame when they occur and nobody is at fault.

## Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. In general, the change is spontaneous (*de novo*) meaning neither parent carried it and the chances of having another child with *GRIN2B*-related neurodevelopmental disorder are very low.

Nonetheless, there is a very small chance that some of the egg cells of the mother or some of the sperm cells of the father do carry the same change in the *GRIN2B* gene. This rare finding is called germline (gonadal) mosaicism. This means that parents who are not found to carry the same *GRIN2B* change as their child when they have a blood test do still have a very small chance of having another child with *GRIN2B*-related neurodevelopmental disorder. We know that this can happen, but it has not been reported for *GRIN2B*-related neurodevelopmental disorder in the medical literature so far.

If the genetic analysis of the parents of a child with *GRIN2B*-related neurodevelopmental disorder shows that one of them has the same change in the gene, the chance of it happening again is much higher. Each family situation is different and a clinical geneticist or genetic counsellor can give specific advice on the chance of recurrence and, if applicable/available, options for testing regarding future pregnancies.

## Management recommendations

Children with *GRIN2B*-related neurodevelopmental disorder should be followed up by a general paediatrician 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.

Consultation with specialists in the fields of ophthalmology and neurology may also be recommended.

Precision medicine approaches targeted at the cellular level are currently under investigation. In some individuals, such experimental therapies yielded (usually mild) benefits regarding behavioural disorders, seizure frequency and development.

## Other things that families say:

### Dribbling

She dribbles a lot, has excess saliva, and chokes or gags on it.

### Teeth

She grinds her teeth.

She has very small, spaced teeth.

She has had extreme teething. Every tooth has come in late, preceded by weeks to months of excruciating pain. When she is experiencing teething pain, her progress seems to stall a bit. All her teeth are in as of age 2½.

### Sleep

She has had very disturbed sleep patterns which remain at the age of 8.

She has a hard time settling down to sleep. We recently installed a camera in her room so I can see that she thrashes around in her crib for a while before falling asleep. She also likes to bite her blankets. Occasionally, she wakes up in the middle of the night and is awake in her crib for an hour. She is generally not upset during these wakeful times.

### Pain

She is very sensitive to pain, such as having her hair brushed or her nails filed.

### Other features reported by families

- Kidney stones, potentially needing surgical removal
- Repeated urine infections
- Spinal curvature (scoliosis) caused in part by low muscle tone, and requiring support and possible later surgery
- Thin, delicate bones, with risk of fracture, and treated with vitamin D supplement
- Squint, requiring monitoring
- Early maturing process, with body hair appearing prematurely

> “She has truly changed our lives for the better. Because of her, we have learned to be more patient and have learned not to sweat the small stuff. She has also opened us up to the whole wide world of disability. Through support groups and playgroups and therapies, we have made so many wonderful new friends that we probably never would have made before any of this. We are far more compassionate and less judgmental because of our daughter’s rare diagnosis.”

## Support Groups

**GRIN2B Foundation** - www.grin2b.com - a parent-run organisation dedicated to furthering research on the *GRIN2B* gene and providing support and education to individuals and families impacted by a *GRIN2B* diagnosis

**CureGRIN** - curegrin.org/ - a foundation founded and run by parents with the goal to find cures and therapies for people around the world suffering from single-gene disorders related to the *GRIN1*, *GRIN2A*, *GRIN2B*, and *GRIN2D* genes

**2BCured** - www.2bcured.org - a partnership between parents and trailblazing experts committed to finding a cure and improving treatment options for *GRIN2B*-related neurodevelopmental disorder

## Facebook Groups

www.facebook.com/grin2b/ - GRIN2B Foundation (public group)

www.facebook.com/groups/grin2bfamilysupport/ - GRIN2B Foundation (private group)

www.facebook.com/groups/All.GRIN/ - 2BCured organisation (private group for researchers and patients)

www.facebook.com/groups/GRIN2B/ - Simons Searchlight (private group)

## Websites

www.patient.info - information on medical conditions and terms

www.nhs.uk/conditions/ - easy to understand explanations of medical conditions and procedures

## Sources and references

The information in this guide is drawn from what is known about children with *GRIN2B*-related neurodevelopmental disorder from the medical literature and information in the *Unique* database. Articles used: Endele 2010; O'Roak 2011, 2012a, 2012b; Lemke 2012; de Ligt 2012; Talkowski 2012; Epi4k consortium 2013; Freuntscht 2013; Hamdan 2014; Kenny 2014; Platzer 2017; Platzer & Lemke 2018 (revised in 2021).

The first-named author and publication date are given to allow you to look for articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). If you wish, you can obtain most articles from *Unique*. In addition, a number of members from *Unique* with *GRIN2B*-related neurodevelopmental disorder helped in the development of this guide by filling out a questionnaire about their child in 2016.

# Notes

## Support and Information

**Rare Chromosome Disorder Support Group,**
The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
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*Unique* lists external message boards and websites in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.
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. *Unique* does its best to keep abreast of changing information and to review its published guides as needed. The text was written by Dr Laura van Dussen, MD, Erfocentrum, Netherlands, and the guide was compiled by *Unique*. This guide was updated in 2022 by Joseph Butt, BSc MSc, and Unique (CA) and reviewed by Dr Johannes R Lemke, MD, Institute of Human Genetics University of Leipzig Medical Center, Germany.

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