**How common are CACNA1A-related disorders?**

CACNA1A-related disorders are very rare. It has been estimated that about 9 people per 100,000 may have a pathogenic CACNA1A variant, there are certainly many more people with this diagnosis than have been described in the medical literature. It is also expected that many more people will be diagnosed over the following years.

**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 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 any lifestyle, dietary or environmental factors. No one is to blame and nobody is at fault.

In most people with CACNA1A-related disorders diagnosed so far, the change in the CACNA1A gene occurred by chance in the child (this is known as **de novo**) and was not found in their parents. However, a few parents have been found to carry a pathogenic CACNA1A gene variant in all or a few (this is known as **mosaicism**) of their cells and it means the variant can be passed on to their child(ren).

**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 CACNA1A gene has been shown to be **de novo**, that means neither parent was found to carry it, the chance of having another child with this gene variant is low (less than 1%). If a parent carries the change (but is not mosaic) the chances of having further children with the genetic change is 50% for each pregnancy. It is also possible to have further children with a CACNA1A-related disorder if a parent is found to be mosaic for the genetic change. A clinical geneticist can give you specific advice for your family.

**Can CACNA1A-related disorders be cured?**

CACNA1A-related disorders cannot be cured at the present time. However, knowing the diagnosis means that appropriate monitoring and treatment can be put in place.

The CACNA1A Foundation has set up a patient registry to collect information that will help connect families, identify research needs, develop standards of care and inform drug development.

**Management recommendations**

Children with CACNA1A-related disorders should be under the care of a multidisciplinary team including the following specialists:
- Geneticist
- Neurologist
- Developmental paediatrician
- Ophthalmologist
- Physio/physical therapist
- Occupational therapist
- Speech and language therapist

Specialist care requirements may change as children progress into adulthood.

**Inform Network Support**

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**Websites, Facebook groups and other links:**

**Website:** www.cacna1a.org
CACNA1A foundation is a parent-led non-profit organisation [501(c)(3)] based in the US dedicated to creating awareness and finding a cure for CACNA1A genetic variants.

**Facebook groups:**
- https://www.facebook.com/cacna1a/
- https://www.facebook.com/groups/cacna1a

*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!

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. This booklet was compiled by Unique (AP) and reviewed by the CACNA1A foundation and Dr Elsa Rossignol, M.D., M.Sc., F.R.C.P., Associate Professor, Departments of Neurosciences and Pediatrics, Université de Montréal, Montréal, Québec, Canada.

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What are CACNA1A-related disorders?

CACNA1A-related disorders are a group of disorders caused by different changes to the same gene - CACNA1A. How each child or adult is affected depends on their specific genetic change but they usually have a spectrum of health and developmental concerns.

What causes CACNA1A-related disorders?

CACNA1A-related disorders are caused by specific changes to a gene called CACNA1A. 

CACNA1A is an abbreviation of the gene’s full name, ‘calcium voltage-gated channel subunit alpha 1A’ which is a description of the protein coded for by the gene. Calcium channels are important for movement of calcium ions into many of our body’s cells, which in turn activates a number of important processes. The CACNA1A protein forms the channels through which the ions move, the channels are known as Ca,2.1. These channels are essential for communication between nerve cells in the brain [they control the release of neurotransmitters], and possibly their survival and ability to change. Calcium ions are also necessary for hormone release, muscle contraction and the regulation of certain genes. The CACNA1A gene is located in the short ‘p’ arm of chromosome 19 in a region called 19p13.13 (shaded pink in the chromosome image below). CACNA1A is positioned in 19p13.2 in older versions of the chromosome 19 DNA sequence).

Genetic changes

Features identified so far in individuals with a CACNA1A-related disorder depend on the specific change to the CACNA1A gene and the functional effect on the Ca,2.1 channel. Some gene variants result in the production of a protein that has a gain of function (GOF), others result in loss of function of the protein (LOF). In both cases, the CACNA1A protein does not function as expected and therefore movement of calcium ions through Ca,2.1 calcium channels does not occur as expected. Activity of the CACNA1A gene can also be affected if the gene has a duplicated section of DNA called a ‘trinucleotide repeat expansion’ or if all or part of the gene is deleted (a 19p13.13 microdeletion/deletion). Gene activity may also be affected by microduplications within the gene.

CACNA1A GOF variants are commonly associated with familial hemiplegic migraine type 1 (FHM1). This is a severe type of migraine with sensory disturbances called aura, and often occurs with sensory loss, visual disturbance, weakness of one side of the body (hemiparesis), repetitive uncontrolled eye movement (nystagmus) and/or movement coordination difficulties (ataxia). Some individuals may also have epilepsy. Some GOF variants do not cause FHM1 but are associated with a severe epilepsy syndrome called Lennox-Gastaut syndrome.

CACNA1A LOF variants are associated with episodic ataxia type 2 (EA2) which involves the sudden occurrence of ataxia, giddiness/loss of balance (vertigo), and/or nausea. Some individuals have migraines, nystagmus and/or epilepsy, some are diagnosed with Lennox-Gastaut syndrome.

CACNA1A trinucleotide repeat expansion is associated with spinocerebellar ataxia type 6 (SCA6), which normally presents later in life [adulthood] with walking difficulties that get worse over time [progressive gait ataxia], lack of coordination (incoordination), involuntary shaking [tremors], difficulty speaking due to affected muscle control [dysarthria], and nystagmus.

CACNA1A deletion (19p13.13 deletion) Chromosome 19p13.13 microdeletions that include the CACNA1A gene have been associated with seizure activity and ataxia in a few children. Children have also been found to have microdeletions of just part of the CACNA1A gene, their features include migraine and ataxia.

CACNA1A duplication (19p13.13 duplication) A microduplication within the CACNA1A gene may disrupt the function of the gene and result in features described above. A duplication of the entire gene is also possible, as is seen in some 19p13.13 duplications, but associated features are not known and will likely be complicated by the presence of additional gene duplications.

Medical and developmental concerns

People with a CACNA1A-related disorder will have one or more of the following features, depending on their genetic change:

- **Global developmental delay (GDD: mild to severe)**
  - Children may be diagnosed with GDD and can be affected in different ways. GDD is a significant delay in cognitive and physical development. It is usually diagnosed when a child is delayed in reaching one or more developmental milestones.

- **Cognitive impairment**
  - Individuals may have trouble concentrating, remembering, learning new things and/or making decisions.

- **Intelectual disability (ID)**
  - Individuals may have limited intellectual abilities and adaptive behavior [social and practical] difficulties.

- **Autism spectrum disorder (ASD)**
  - ASD is a term used to describe a group of developmental disorders that affect communication and behavior. Individuals may be diagnosed with ASD or as having autistic like features.

- **Muscle tone**
  - Some children have poor muscle control, this is known as hypotonia and can also affect feeding abilities. Children who have GOF variants and epilepsy/Lennox-Gastaut syndrome typically have spasticity and increased muscle tone [hypertonia].

- **Seizures (mild to severe)**
  - Seizures are sudden and uncontrolled electrical disturbances in the brain and come in many forms. Some people with a CACNA1A-related disorder experience seizures and epilepsy.

- **Balance and coordination difficulties (ataxia)**
  - Individuals may have difficulties with gross motor skills, balancing and performing tasks that require coordination, such as walking; some benefit from the use of a wheelchair.

- **Migraines**
  - Migraines are common in children and adults with CACNA1A GOF variants but can also be experienced by people with other CACNA1A changes.

- **Neuron loss (cerebellar atrophy)**
  - Some individuals may have a certain amount of neuron loss in brain tissue, and loss of connections between neurons.

- **Eye disorder**
  - An involuntary upward movement of the eyes known as paroxysmal tonic upgaze (PTU) has been identified in some individuals with a CACNA1A-related disorder, as has nystagmus.

- **Stroke**
  - A few children have had stroke like episodes [SLE] or an ischemic stroke but this is very rare and occurred in children with a GOF variant and FHM1 following a minor head trauma.