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 and 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!

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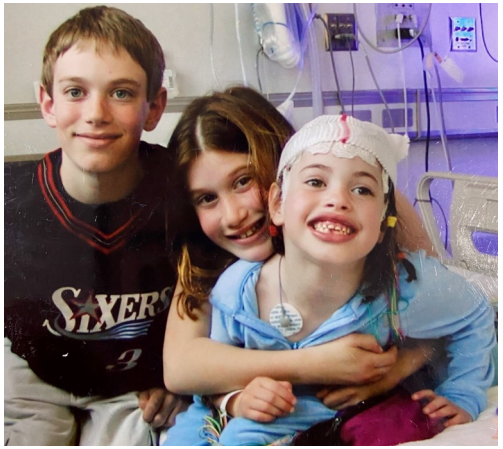
Understanding Chromosome & Gene Disorders

CACNA1A-related disorders



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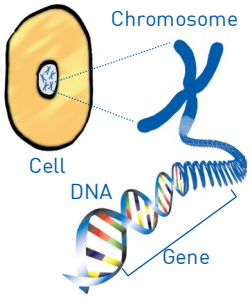
What are *CACNA1A*-related disorders?

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?

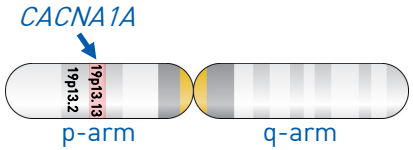


CACNA1A-related disorders are caused by specific changes to a gene called *CACNA1A*.

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 $Ca_v2.1$. 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).



Chromosome 19

We have two copies of chromosome 19 in our cells, so we also have two copies of the *CACNA1A* gene. *CACNA1A*-related disorders occur when only one copy of the *CACNA1A* gene is affected, this is known as autosomal dominant since the change occurred on an autosome (this means any of our chromosomes numbered 1-22) and features are apparent when only one copy of the gene is altered (dominant).

CACNA1A has a specific pattern of activity in different parts of the brain, especially during development, so changes to its function may cause significant neurological difficulties.

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 $Ca_v2.1$ 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 $Ca_v2.1$ 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.

Intellectual 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.