

How common are *CASK*-related disorders?

CASK-related disorders are very rare. Currently (in 2022) less than 150 people, mostly children, with this diagnosis have been reported in the medical literature. It is expected that more people 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, random rare changes may occur in the genetic material of the egg and/or sperm that make a new child. Such changes are part of the child's genome but they 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 particular genes or specific parts of a chromosome are affected that there is an impact on health and/or development.

In most children diagnosed with a *CASK*-related disorder so far, the change in the *CASK* gene occurred by chance in that child (this is known as *de novo*) and was not found in their parents. Very few children are known to have inherited a hypomorphic variant 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 *CASK* gene has been shown to be *de novo*, meaning neither parent was found to carry it, the chance of having another child with a *CASK*-related disorder is very low. 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 passing on the *CASK* variant to a child is 50% for each pregnancy. A clinical geneticist or genetic counsellor can give you specific advice for your family.

Can it be cured?

CASK-related disorders cannot be cured at the present time; however, knowing the diagnosis means that appropriate monitoring and treatment can be put in place, especially for features of medical concern such as seizures.

Families say

“ My daughter has MICPCH caused by a *CASK* gene mutation. Since there was little information available and an obvious need for more research, I founded the UK based *CASK* Research Foundation. The foundation aims to financially support scientific research, support families, raise awareness and arrange an annual family meet up (UK). ”

“ As a baby, our daughter was diagnosed with microcephaly and delayed myelination. It would take many more tests, appointments, and sleepless nights before her *CASK* Gene diagnosis came at 8 years old. When other families receive this life changing news, we want them to quickly find hope for a life as beautiful as hers has become through her hard work. This hope and the sense of community we found online prompted us to create The *CASK* Gene Foundation (US). ”

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!

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 booklet was compiled by UniquE (AP) and verified by Prof. Dr. Ute Moog, MD, PhD, Clinical Geneticist, Institute of Human Genetics, Heidelberg University Hospital, Germany.

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Understanding Chromosome & Gene Disorders

CASK-related disorders (including Xp11.14 deletions or duplications containing part of the *CASK* gene)



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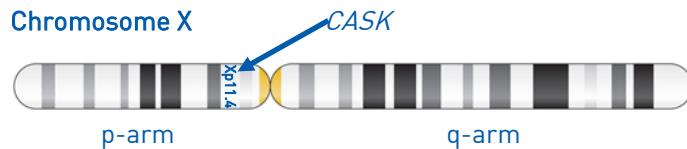
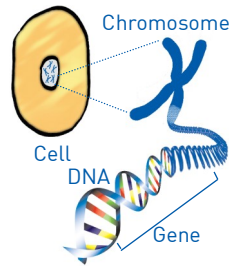
What are *CASK*-related disorders?

CASK-related disorders are rare genetic conditions that cause developmental delay and intellectual disability. As is common with genetic conditions, each person can be affected differently. This depends on a number of factors such as the type of genetic change and whether the person is male or female. *CASK*-related disorders are also associated with different types of seizure, lack of or limited speech and difficulties with mobility and coordination.

What causes *CASK*-related disorders?

CASK-related disorders are caused by specific changes (known as **pathogenic variants**) in a gene called *CASK*. **Deletions** or **duplications** within the gene, that disrupt its function, or those containing the whole gene can also cause a *CASK*-related disorder.

The *CASK* gene is located on the short 'p' arm of the X chromosome in a region called Xp11.4 (see below).



(*CASK* is an abbreviation of the gene's full name, calcium/calmodulin-dependent serine protein kinase.)

Genetic changes that cause the gene to stop working are called 'loss of function' (LOF) variants; changes that cause the gene to have a **reduced function** are called **hypomorphic variants**.

The *CASK* gene codes for the *CASK* protein which has many different roles in our cells. The *CASK* protein binds together with other proteins to form complexes with different functions. These functions are not all fully understood and vary greatly, from controlling the expression of other genes, to forming the junction between nerve cells (called synapses) that are required to transmit signals. Perhaps the most important roles are those that involve the development, function and maintenance of the brain and nervous system.

CASK-related disorders in females

■ Two X chromosomes

Females usually have two X chromosomes and so have two copies of the *CASK* gene. Girls with a change to their *CASK* gene also have an unaffected copy of the gene on their second X chromosome that can partially compensate for the loss or altered function of the affected gene copy. However, one X chromosome in each cell is 'inactivated' and the effect of X-inactivation on *CASK*-related disorders in girls is not yet fully understood.

■ LOF variants

Girls who have a change to one copy of their *CASK* gene that causes a loss of function will have moderate to severe **intellectual disability (ID)** and progressive **microcephaly** (a small head and brain) with underdevelopment of specific parts of the brain called the pons and the cerebellum. This is known as **microcephaly with pontine and cerebellar hypoplasia (MICPCH)**. Symptoms and features can also include:

- absent or severely impaired speech in most girls and difficulties using alternative means of communication
- about 25% of girls will learn to walk unassisted, but the majority will require mobility equipment
- seizures: about 40% of girls have seizures before the age of 10 years that can be hard to control (intractable)
- weak muscle tone (hypotonia)
- tight muscle tone in legs and/or arms (hypertonia/spasticity)
- difficulties sitting independently in a few girls
- movement disorders e.g. dystonia (unintended muscle contractions)
- eye and/or sight anomalies
- sensorineural hearing loss
- sleep disturbances
- hand stereotypies (and self biting)
- short stature

■ Hypomorphic variants

Females who have a change in one copy of their *CASK* gene, that causes it to have a reduced function, can be relatively unaffected with intelligence within the standard range or they can have ID (which can be mild to severe). They may also have an eye anomaly, which can vary, and/or other features (that have been found in a few but not all girls).

CASK-related disorders in males

■ One X chromosome

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 *CASK* gene. If the gene is altered in any way, then boys do not have a second copy to compensate for the loss (LOF) or altered (hypomorphic) function.

■ LOF variants

Boys with a genetic variant that cause a loss of function of the *CASK* gene are sadly lost during pregnancy or only survive for a few months after birth. These boys usually have MICPCH, severe intractable epilepsy with severe to profound developmental delay or no development. Some boys however do not have the genetic change in all of their cells, this is known as **mosaicism** and means that boys can survive. These boys have MICPCH, severe epilepsy and developmental delay with ID, similar to the symptoms and features seen in girls.

■ Hypomorphic variants

Boys who have a genetic change to their only copy of the *CASK* gene that causes it to have a reduced function are likely to survive and can have a broad spectrum of symptoms and features. These involve a range of severities from mild ID to severe ID and MICPCH with or without eye anomalies, such as involuntary eye movement (nystagmus), and seizures. They may also have other clinical features such as severe weak muscle tone (hypotonia).

Symptoms and features are likely to depend on how the *CASK* protein has been altered as well as possibly each child's own unique genetic background. How a child is affected will also depend on whether all cells of their body (known as somatic cells) carry the variant. If only some of the body's cells carry the variant, this is known as **somatic mosaicism**.

Management recommendations

Children with a *CASK*-related disorder should be under the care of a multidisciplinary team including a Paediatrician, Geneticist and the Community Paediatric team with neuro-developmental paediatrician, physiotherapy, occupational therapy and speech and language therapy. Children should be referred to an Ophthalmologist (eye doctor) and ENT specialist (ear doctor) for assessment.