

# SLC35A2-Congenital Disorder of Glycosylation

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*SLC35A2*-congenital disorder of glycosylation (*SLC35A2*-CDG, formerly known as congenital disorder of glycosylation type II<sub>m</sub>) is an inherited condition that causes neurological problems and other abnormalities. This disorder's signs and symptoms and their severity vary among affected individuals.

Keywords: genetic conditions

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## 1. Introduction

Individuals with *SLC35A2*-CDG typically develop signs and symptoms of the condition early in infancy. Seizures develop within the first months of life, usually involving uncontrollable muscle stiffening (infantile spasms) that can switch to shorter episodes of muscle jerks (epileptic spasms) later in childhood. In some individuals, the seizures do not improve with anti-epileptic medications. Individuals with *SLC35A2*-CDG often have abnormal brain function (encephalopathy), unusual facial features, skeletal abnormalities, and weak muscle tone (hypotonia) with poor head control. They also have severe intellectual disability and delayed development, often only being able to sit or crawl and never developing meaningful speech. Affected children may have feeding difficulties and fail to grow or gain weight at the expected rate. Some have vision or hearing problems.

In *SLC35A2*-CDG, medical imaging shows loss of tissue (atrophy) in parts of the brain called the cerebrum and cerebellum. These brain regions are necessary for thinking ability, hearing, vision, emotion, and coordinated movement. There can also be thinning of the tissue that connects the left and right halves of the brain (the corpus callosum) or a fluid-filled sac (cyst) on the membrane that surrounds the brain (arachnoid pouch).

## 2. Frequency

*SLC35A2*-CDG is a rare disorder. At least nine affected individuals have been described.

## 3. Causes

Mutations in the *SLC35A2* gene cause *SLC35A2*-CDG. This gene provides instructions for making an enzyme that is involved in a process called glycosylation. During this process, complex chains of sugar molecules (oligosaccharides) are added to proteins and fats (lipids). Glycosylation modifies proteins and lipids so they can fully perform their functions. The enzyme produced from the *SLC35A2* gene transfers a simple sugar called galactose to growing oligosaccharides at a particular step in the formation of the sugar chain. Once the correct number of sugar molecules are linked together, the oligosaccharide is attached to a protein or lipid.

*SLC35A2* gene mutations lead to the production of an abnormal enzyme with reduced or no activity. Without a properly functioning enzyme, glycosylation cannot proceed normally, and oligosaccharides are incomplete. The signs and symptoms of *SLC35A2*-CDG are likely due to impaired glycosylation of proteins and fats that are needed for the normal function of various organs and tissues.

In some individuals with *SLC35A2*-CDG, glycosylation becomes normal later in childhood. The cause of this apparent correction is unknown. The restoration of glycosylation in these individuals, however, does not seem to improve the signs and symptoms of *SLC35A2*-CDG.

### 3.1. The Gene Associated with *SLC35A2*-Congenital Disorder of Glycosylation

- *SLC35A2*

## 4. Inheritance

*SLC35A2*-CDG is inherited in an X-linked dominant pattern. The *SLC35A2* gene is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell is thought to be incompatible with life. A few males with *SLC35A2*-CDG have a mutation in only some of the body's cells, a situation known as mosaicism. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. Usually X-inactivation occurs randomly, so that each X chromosome is active in about half the body's cells. Sometimes X-inactivation is not random, and one X chromosome is active in more than half of cells. When X-inactivation does not occur randomly, it is called skewed X-inactivation.

In *SLC35A2*-CDG, skewed X-inactivation allows for the normal copy of the gene to be active (expressed) and leads to the production of the normal enzyme in most cells in affected females. However, it is thought that X inactivation in nerve cells in the brain might not be skewed and so the mutated *SLC35A2* gene is expressed in these cells. As a result, little or no functional enzyme is present in nerve cells, leading to the various neurological features of *SLC35A2*-CDG.

## 5. Other Names for This Condition

- CDG IIIm
- CDG syndrome type IIIm
- CDG-IIIm
- CDG2M
- CDGIIIm
- congenital disorder of glycosylation, type IIIm
- EIEE22
- epileptic encephalopathy, early infantile, 22
- *SLC35A2*-CDG

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