2-hydroxyglutaric aciduria

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2-hydroxyglutaric aciduria is a condition that causes progressive damage to the brain. The major types of this disorder are called D-2-hydroxyglutaric aciduria (D-2-HGA), L-2-hydroxyglutaric aciduria (L-2-HGA), and combined D,L-2-hydroxyglutaric aciduria (D,L-2-HGA).

genetic conditions

1. Introduction

The main features of D-2-HGA are delayed development, seizures, weak muscle tone (hypotonia), and abnormalities in the largest part of the brain (the cerebrum), which controls many important functions such as muscle movement, speech, vision, thinking, emotion, and memory. Researchers have described two subtypes of D-2-HGA, type I and type II. The two subtypes are distinguished by their genetic cause and pattern of inheritance, although they also have some differences in signs and symptoms. Type II tends to begin earlier and often causes more severe health problems than type I. Type II may also be associated with a weakened and enlarged heart (cardiomyopathy), a feature that is typically not found with type I.

L-2-HGA particularly affects a region of the brain called the cerebellum, which is involved in coordinating movements. As a result, many affected individuals have problems with balance and muscle coordination (ataxia). Additional features of L-2-HGA can include delayed development, seizures, speech difficulties, and an unusually large head (macrocephaly). Typically, signs and symptoms of this disorder begin during infancy or early childhood. The disorder worsens over time, usually leading to severe disability by early adulthood.

Combined D,L-2-HGA causes severe brain abnormalities that become apparent in early infancy. Affected infants have severe seizures, weak muscle tone (hypotonia), and breathing and feeding problems. They usually survive only into infancy or early childhood.

2. Frequency

2-hydroxyglutaric aciduria is a rare disorder. D-2-HGA and L-2-HGA have each been reported to affect fewer than 150 individuals worldwide. Combined D,L-2-HGA appears to be even rarer, with only about a dozen reported cases.

3. Causes

The different types of 2-hydroxyglutaric aciduria result from mutations in several genes. D-2-HGA type I is caused by mutations in the *D2HGDH* gene; type II is caused by mutations in the *IDH2* gene. L-2-HGA results from mutations in the *L2HGDH* gene. Combined D,L-2-HGA is caused by mutations in the *SLC25A1* gene.

The *D2HGDH* and *L2HGDH* genes provide instructions for making enzymes that are found in mitochondria, which are the energy-producing centers within cells. The enzymes break down compounds called D-2-hydroxyglutarate and L-2-hydroxyglutarate, respectively, as part of a series of reactions that produce energy for cell activities. Mutations in either of these genes lead to a shortage of functional enzyme, which allows D-2-hydroxyglutarate or L-2-hydroxyglutarate to build up in cells. At high levels, these compounds can damage cells and lead to cell death. Brain cells appear to be the most vulnerable to the toxic effects of these compounds, which may explain why the signs and symptoms of D-2-HGA type I and L-2-HGA primarily involve the brain.

The *IDH2* gene provides instructions for making an enzyme in mitochondria that normally produces a different compound. When the enzyme is altered by mutations, it takes on a new, abnormal function: production of the potentially toxic compound D-2-hydroxyglutarate. The resulting excess of this compound damages brain cells, leading to the signs and symptoms of D-2-HGA type II. It is unclear why an accumulation of D-2-hydroxyglutarate may be associated with cardiomyopathy in some people with this form of the condition.

The *SLC25A1* gene provides instructions for making a protein that transports certain molecules, such as citrate, in and out of mitochondria. Mutations in the *SLC25A1* gene reduce the protein's function, which prevents it from carrying out this transport. Through processes that are not fully understood, a loss of this transport allows both D-2-hydroxyglutarate and L-2-hydroxyglutarate to build up, which damages brain cells. Researchers suspect that an imbalance of other molecules, particularly citrate, also contributes to the severe signs and symptoms of combined D,L-2-HGA.

3.1. The genes associated with 2-hydroxyglutaric aciduria

- D2HGDH
- IDH2
- L2HGDH
- SLC25A1

4. Inheritance

D-2-HGA type I, L-2-HGA, and combined D,L-2-HGA all have an autosomal recessive pattern of inheritance, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

D-2-HGA type II is considered an autosomal dominant disorder because one copy of the altered gene in each cell is sufficient to cause the condition. The disorder typically results from a new mutation in the *IDH2* gene and occurs in people with no history of the condition in their family.

5. Other Names for This Condition

- 2-HGA

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