ASPA Gene

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aspartoacylase

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1. Normal Function

The *ASPA* gene provides instructions for making an enzyme called aspartoacylase. In the brain, this enzyme breaks down a compound called N-acetyl-L-aspartic acid (NAA) into aspartic acid (an amino acid that is a building block of many proteins) and another molecule called acetic acid.

The production and breakdown of NAA appears to be critical for maintaining the brain's white matter, which consists of nerve fibers surrounded by a myelin sheath. The myelin sheath is the covering that protects nerve fibers and promotes the efficient transmission of nerve impulses. The precise function of NAA is unclear. Researchers had suspected that it played a role in the production of the myelin sheath, but recent studies suggest that NAA does not have this function. The enzyme may instead be involved in the transport of water molecules out of nerve cells (neurons).

2. Health Conditions Related to Genetic Changes

Canavan disease

More than 80 mutations in the *ASPA* gene are known to cause Canavan disease, which is a rare inherited disorder that affects brain development. Researchers have described two major forms of this condition: neonatal/infantile Canavan disease, which is the most common and most severe form, and mild/juvenile Canavan disease. The *ASPA* gene mutations that cause the neonatal/infantile form severely impair the activity of aspartoacylase, preventing the breakdown of NAA and allowing this substance to build up to high levels in the brain. The mutations that cause the mild/juvenile form have milder effects on the enzyme's activity, leading to less accumulation of NAA.

An excess of NAA in the brain is associated with the signs and symptoms of Canavan disease. Studies suggest that if NAA is not broken down properly, the resulting chemical imbalance interferes with the formation of the myelin sheath as the nervous system develops. A buildup of NAA also leads to the progressive destruction of existing myelin sheaths. Nerves without this protective covering malfunction, which disrupts normal brain development.

While Canavan disease occurs in people of all ethnic backgrounds, it is most common in people of Ashkenazi (eastern and central European) Jewish heritage. Two specific *ASPA* gene mutations cause almost all cases of the disease in people of Ashkenazi Jewish descent. One of these mutations replaces the amino acid glutamic acid with the amino acid alanine at position 285 of the enzyme (written as Glu285Ala or E285A). This genetic change greatly reduces the amount of functional aspartoacylase. The other mutation, which is written as Tyr231Ter or Y231X, prematurely stops protein production and leads to an abnormally small, nonfunctional version of the enzyme.

A different *ASPA* gene mutation is most common in people who are not of Ashkenazi Jewish descent. This mutation substitutes the amino acid glutamic acid for the amino acid alanine at position 305 of aspartoacylase (written as Ala305Glu or A305E). This mutation also leads to the production of a nonfunctional version of the enzyme.

3. Other Names for This Gene

- ACY2
- ACY2_HUMAN
- aminoacylase 2
- aminoacylase II

- ASP
- N-acyl-L-aspartate amidohydrolase

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