ALDH18A1 gene

aldehyde dehydrogenase 18 family member A1

Normal Function

The *ALDH18A1* gene provides instructions for making a protein known as P5CS. This protein is found in cell structures called mitochondria, which are the energy-producing centers of cells. P5CS appears to be important for mitochondrial function, and it plays a role in the formation (synthesis) of the protein building block (amino acid) proline.

The formation of proline is a multi-step process that converts the amino acid glutamate to the amino acid proline. The P5CS protein carries out the first step in this process by converting the amino acid glutamate to glutamate 5-semialdehyde. Subsequent steps convert this intermediate product to the amino acid proline. The conversion of glutamate to proline is important in maintaining a supply of the amino acids needed for protein production and for energy transfer within the cell.

Health Conditions Related to Genetic Changes

Cutis laxa

Variants (also known as mutations) in the *ALDH18A1* gene can cause two different types of cutis laxa: autosomal dominant cutis laxa type 3 (ADCL3) and autosomal recessive cutis laxa type 3A (ARCL3A, which is also known as de Barsy syndrome). In autosomal dominant cutis laxa, one copy of the altered *ALDH18A1* gene in each cell is sufficient to cause the characteristic features of the disorder. In autosomal recessive cutis laxa, both copies of the gene in each cell must be altered to result in the condition. These types of cutis laxa feature loose, wrinkled, and sagging skin that is often described as parchment-like; prominant veins; loose joints; clouding of the lenses of the eyes (cataracts) or other eye abnormalities; intellectual disability; and movement problems that can worsen over time. Autosomal recessive cutis laxa tends to be more severe than autosomal dominant.

Most *ALDH18A1* gene variants involved in cutis laxa result in production of a P5CS protein with reduced activity. Some studies suggest that in ADCL3A, the abnormal protein from the altered copy of the gene interferes with the protein produced from the normal copy, further reducing the activity of this protein in cells. While the amount of proline is reduced in some people with *ALDH18A1* gene variants, the levels are normal in other affected individuals. Impairment of the P5CS protein may disrupt mitochondrial

function, which could lead to the death of skin and nerve cells. However, it is unclear exactly how changes in the *ALDH18A1* gene lead to the particular signs and symptoms of cutis laxa.

Other disorders

Variants in the *ALDH18A1* gene can cause autosomal dominant spastic paraplegia type 9A (SPG9A) and autosomal recessive spastic paraplegia type 9B (SPG9B). These conditions are part of a group of genetic disorders known as hereditary spastic paraplegias, which are characterized by muscle stiffness (spasticity) and the development of paralysis of the lower limbs (paraplegia) caused by breakdown of nerve cells that trigger muscle movement (motor neurons). Other features of SPG9A or SPG9B can include clouding of the lenses of the eyes (cataracts), developmental delay, or intellectual disability.

The *ALDH18A1* gene variants are thought to reduce the function of the P5CS protein. Researchers suspect that impairment of the proline synthesis pathway hinders energy production in mitochondria, which may contribute to the death of neurons and lead to the progressive movement problems of SPG9A and SPG9B; however, the exact mechanism that causes these conditions is unknown.

Other Names for This Gene

- GSAS
- PYCS
- pyrroline-5-carboxylate synthetase (glutamate gamma-semialdehyde synthetase)

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ALDH18A1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5832[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=ALDH18A1)

Catalog of Genes and Diseases from OMIM

- ALDEHYDE DEHYDROGENASE 18 FAMILY, MEMBER A1; ALDH18A1 (https://omim.org/entry/138250)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5832)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=ALDH18A1[gene])

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