PSEN1 gene

presenilin 1

Normal Function

The *PSEN1* gene provides instructions for making a protein called presenilin 1. This protein is one part (subunit) of a complex called gamma- (γ-) secretase. Presenilin 1 carries out the major function of the complex, which is to cut apart (cleave) other proteins into smaller pieces called peptides. This process is called proteolysis, and presenilin 1 is described as the proteolytic subunit of γ-secretase.

The γ-secretase complex is located in the membrane that surrounds cells, where it cleaves many different proteins that span the cell membrane (transmembrane proteins). This cleavage is an important step in several chemical signaling pathways that transmit signals from outside the cell into the nucleus. One of these pathways, known as Notch signaling, is essential for the normal growth and maturation (differentiation) of hair follicle cells and other types of skin cells. Notch signaling is also involved in normal immune system function.

The γ-secretase complex may be best known for its role in processing amyloid precursor protein (APP), which is made in the brain and other tissues. γ-secretase cuts APP into smaller peptides, including soluble amyloid precursor protein (sAPP) and several versions of amyloid-beta (β) peptide. Evidence suggests that sAPP has growth-promoting properties and may play a role in the formation of nerve cells (neurons) in the brain both before and after birth. Other functions of sAPP and amyloid-β peptide are under investigation.

Health Conditions Related to Genetic Changes

Alzheimer's disease

Dozens of *PSEN1* gene variants (also known as mutations) have been identified in patients with early-onset Alzheimer's disease, a degenerative brain condition that begins before age 65. Variants in the *PSEN1* gene are the most common cause of early-onset Alzheimer's disease, accounting for up to 70 percent of cases.

Almost all *PSEN1* gene variants change single building blocks of DNA (nucleotides) in a particular segment of the *PSEN1* gene. These variants result in the production of an abnormal presenilin 1 protein. Defective presenilin 1 interferes with the function of the γ-

secretase complex, which alters the processing of APP and leads to the overproduction of a longer, toxic version of amyloid-β peptide. Copies of this protein fragment stick together and build up in the brain, forming clumps called amyloid plaques that are a characteristic feature of Alzheimer's disease. A buildup of toxic amyloid-β peptide and the formation of amyloid plaques likely lead to the death of neurons and the progressive signs and symptoms of Alzheimer's disease.

Hidradenitis suppurativa

At least one variant (also known as a mutation) in the *PSEN1* gene has been found to cause hidradenitis suppurativa, a chronic skin disease characterized by recurrent boil-like lumps (nodules) under the skin that develop in hair follicles. The nodules tend to become inflamed and painful, and they produce significant scarring as they heal.

The identified variant deletes a single DNA building block (nucleotide) from the *PSEN1* gene, written as 725delC. This genetic change reduces the amount of functional presenilin 1 produced in cells, so less of this protein is available to act as part of the γ-secretase complex. The resulting shortage of normal γ-secretase impairs cell signaling pathways, including Notch signaling. Although little is known about the mechanism, studies suggest that abnormal Notch signaling may promote the development of recurrent nodules in hair follicles and trigger inflammation in the skin.

Studies suggest that the *PSEN1* gene variant that causes hidradenitis suppurativa has a different effect on γ-secretase function than the variants that cause early-onset Alzheimer's disease. These differences may explain why no single *PSEN1* gene variant has been reported to cause the signs and symptoms of both diseases.

Familial dilated cardiomyopathy

MedlinePlus Genetics provides information about Familial dilated cardiomyopathy

Other Names for This Gene

- AD3
- FAD
- presenilin 1 (Alzheimer disease 3)
- presenilin 1 protein
- PS1
- PSN1_HUMAN
- PSNL1 gene product
- S182 protein

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PSEN1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5663[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28PSEN1%5BTI%5D%29+OR+%28presenilin+1%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PRESENILIN 1; PSEN1 (https://omim.org/entry/104311)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5663)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PSEN1[gene])

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Genomic Location

The *PSEN1* gene is found on chromosome 14 (https://medlineplus.gov/genetics/chromosome/14/).

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