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# Gene Section
## Review

# PSEN2 (presenilin 2 (Alzheimer disease 4))

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## Identity

**Other names: AD3L, AD4, PS2, STM2**
**HGNC (Hugo): PSEN2**
**Location: 1q42.13**

## DNA/RNA

### Description

Twelve exons, spans approximately 26.7 kb of genomic DNA in the centromere to telomere orientation, the translation initation codon is in exon 4 and the stop codon in exon 12.

### Transcription

mRNA of approximately 2.3 kb. Two alternatively spliced transcript variants encoding different isoforms of PSEN2 have been identified.

### Pseudogene

Not known.

## Protein

### Description

The open reading frame encodes a 448 amino acid protein, with an estimated molecular weight of 50 kDa. It is a multi-spanning transmembrane protein with a predicted 9 transmembrane domains. Heterogeneous proteolytic processing generates N-terminal and C-terminal fragments.

### Expression

Neuronal (higher levels in hippocampus and cerebellum). Isoform 1 is seen in the placenta, skeletal muscle and heart while isoform 2 is seen in the heart, brain, placenta, liver, skeletal muscle and kidney. (In isoform 2 amino-acids 263-296 are missing).

### Localisation

Endoplasmic reticulum, plasma membrane, golgi apparatus.

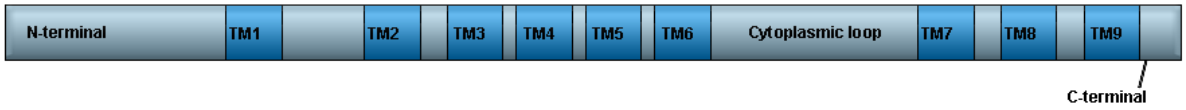
### Function

Catalytic core of the gamma-secretase complex. This complex catalyses the intramembrane cleavage of single-pass membrane proteins such as Notch and the Amyloid Precursor Protein (APP) to give intracellular signaling. The released intracellular domains of Notch or APP form complexes with other proteins to regulate gene transcription.

### Homology

The PSEN2 gene is conserved in chimpanzee, dog, cow, mouse, rat, chicken, and zebrafish.


Presenilin 2 transcript, lines indicate introns and boxes exons. Untranslated regions are represented as yellow boxes and coding regions as red boxes.




Presenilin 2 protein domains, bright blue boxes are transmembrane domains (TM).

# Mutations

## Somatic

23 mutations.

| Nucleotide change | Disease | Reference |
|---|---|---|
| Arg62His | AD | Cruts et al., 1998; Guerreiro et al., 2008 |
| Arg71Trp | AD | Guerreiro et al., 2008 |
| Thr122Pro | AD | Finckh et al., 2000; 2005 |
| Ser130Leu | AD | Sorbi et al., 2002; Tedde et al., 2003; Tomaino et al., 2007 |
| Val139Met | AD | Bernardi et al., 2008 |
| Asn141Ile | AD | Levy-Lahad et al., 1995; Rogaev et al., 1995 |
| Met174Val | AD | Guerreiro et al., 2008 |
| Ser175Cys | AD | Piscopo et al., 2008 |
| Gln228Leu | AD | Zekanowski et al., 2003 |
| Met239Ile | AD | Finckh et al., 2000 |
| Met239Val | AD | Rogaev et al., 1995; Marcon et al., 2004 |
| Val393Met | AD | Lindquist et al., 2008; 2009 |
| Thr430Met | AD | Lleo et al., 2002; Ezquerra et al., 2003 |
| Asp439Ala | AD | Lleo et al., 2001; 2002 |
| Arg62His | Breast Cancer | To et al., 2006 |
| Arg71Trp | Breast Cancer | To et al., 2006 |
| Tyr231Cys | FTD | Marcon et al., 2008; 2009 |
| Ala85Val | LBD | Piscopo et al., 2008 |
| Thr122Arg | Atypical Dementia | Binetti et al., 2003 |

**Table. Mutations identified through genetic screening.** AD: Alzheimer's Disease, FTD: Frontotemporal Dementia, LBD: Lewy Body Dementia.

# Implicated in

## Breast cancer

**Disease**

Breast cancer is the most common form of cancer for women. The cancer originates from the breast tissue where it can be a ductal carcinoma or lobular carcinoma. They can be further defined as in situ or invasive cancers.

**Oncogenesis**

Mutations (see above).

## Alzheimer's disease

**Note**

Mutations (see above) taken from the Alzheimer's Disease and Frontotemporal Dementia Mutation Database. Only pathogenic mutations are included.

**Disease**

Alzheimer's disease is the most prevalent form of dementia. In affected individuals the disease causes a progressive and permanent decline in memory and cognitive abilities. Neuropathogenesis is proposed to be a result of the accumulation of amyloid-beta peptides in the brain together with increased oxidative stress and neuroinflammation. The presenilin proteins are central to the gamma-secretase cleavage of the amyloid precursor protein (APP), releasing the amyloid-beta peptide. Point mutations in the presenilin genes lead to cases of familial Alzheimer's disease (and some sporadic cases) by altering APP cleavage resulting in excess amyloid-beta formation.

## Frontotemporal Dementia (FTD)

**Note**

Mutation (see above).

**Disease**

Frontotemporal dementia is a group of related conditions resulting from the progressive degeneration of the temporal and frontal lobes of the brain (frontotemporal lobar degeneration, FTLD), usually with the presence of abnormal intracellular protein accumulations. These areas of the brain play a significant role in decision-making, behavioral control, emotion and language. The disorder is often sporadic, familial FTD has been linked to mutations in several genes, including those encoding the microtubule-associated protein tau (MAPT), progranulin (GRN), valosin-containing protein (VCP) and charged multivescicular body protein 2B (CHMP2B).

## Lewy body Dementia (DLB)

**Note**

Mutation (see above).

**Disease**

Dementia with Lewy bodies is a neurodegenerative disorder associated with abnormal structures (Lewy bodies) which are clumps of alpha-synuclein and ubiquitin protein in neurons found in certain areas of the brain. In addition to dementia, patients with dementia with Lewy bodies experience hallucinations, motor impairment, and fluctuating alertness.


Diagram taken from http://www.molgen.ua.ac.be/ADMutations. Coloured circles indicate mutation sites. Red: pathogenic, orange: pathogenic nature unclear, green: not pathogenic.

## To be noted

**Note**

Truncated variant PSEN2 protein (PS2V). Variant transcript lacks exon 5 due to alternative splicing. Encodes the first 119 codons of PSEN2 plus a newly generated five amino acids SSMAG. PS2V is detected in sporadic Alzheimer's disease, bi-polar and schizophrenia cases (Sato et al., 1999; Smith et al., 2004). Cell-culture experiments indicate that this variant is upregulated under hypoxic conditions (Sato et al., 1999).

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