Mutations in presenilin 2 and its implications in Alzheimer’s disease and other dementia-associated disorders

Abstract: Alzheimer’s disease (AD) is the most common form of dementia. Mutations in the genes encoding presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein have been identified as the main genetic causes of familial AD. To date, more than 200 mutations have been described worldwide in PSEN1, which is highly homologous with PSEN2, while mutations in PSEN2 have been rarely reported. We performed a systematic review of studies describing the mutations identified in PSEN2. Most PSEN2 mutations were detected in European and in African populations. Only two were found in Korean populations. Interestingly, PSEN2 mutations appeared not only in AD patients but also in patients with other disorders, including frontotemporal dementia, dementia with Lewy bodies, breast cancer, dilated cardiomyopathy, and Parkinson’s disease with dementia. Here, we have summarized the PSEN2 mutations and the potential implications of these mutations in dementia-associated disorders.

Keywords: mutations in presenilin 2, Alzheimer’s disease

Introduction

Alzheimer’s disease (AD) is the most common form of neurodegenerative disease of the brain. Pathological hallmarks of AD include intraneuronal accumulation of paired helical filaments composed of abnormal tau proteins and extracellular deposits of β-amyloid peptide (Aβ) in neuritic plaques. Clinically, AD can be categorized into two phenotypes based on the ages of onset: early-onset AD (EOAD; <65 years) and late-onset AD (LOAD; >65 years), of which LOAD is the more common form worldwide. The proportion of EOAD in all AD cases is between 5% and 10%. Presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) are mostly associated with autosomal dominant forms of EOAD. Apart from genetic factors, mutations are environmentally related. Genetic–environmental interactions may be caused by variation in the age of onset, neuropathological patterns, and disease duration. To date, more than 200 mutations have been described in PSEN1 throughout the world, but mutations in PSEN2 are extremely rare. Less than 40 mutations in PSEN2 have been identified. From those, two PSEN2 mutations were detected in Korean patients. Unlike PSEN1, AD patients with PSEN2 mutations have a wide range in the age of onset, from 40 to 80 years. Interestingly, some reports have suggested that the inherited mode of AD was autosomal inheritance with variable penetrance, which suggests that other environmental factors might also be significant for AD pathogenesis. In addition, mutations in PSEN2 are also closely involved in other diseases, including EOAD, LOAD, frontotemporal dementia (FTD), dementia with Lewy bodies (DLBs), breast cancer, dilated cardiomyopathy (DCM). In this review,
we studied and summarized PSEN2, in particular, the known PSEN2 mutations and the potential implications of PSEN2 in AD and in other disorders.

**PSEN2 gene**

In 1995, PSEN2 was initially reported as a causative gene for AD, following the identification of APP and PSEN1. The gene was localized to chromosome 1q42.13. It consists of 12 exons, of which exon 1 and exon 2 contain the untranslated regions.

**PSEN2 transcription**

**Transcriptional regulation**

PSEN2 is driven by two separate promoter elements, P1 and P2, which are located in exon 1 and exon 2, respectively. The upstream P1 is a housekeeping promoter. PSEN2-P1 activity depends on a stimulating protein 1 binding site at the most 5’ initiation site. The downstream P2 is induced by Egr-1, which represses PSEN2-P1 activity. Interestingly, a study showed that Egr-1 cannot regulate the PSEN2 promoter in mouse. APP influences the expression of Egr-1 by enhancing histone H4 acetylation of the Egr-1 promoter.

**Splice variant**

The two isoforms of PSEN2 protein are produced by alternative splicing. An aberrant splice variant of PSEN2 lacks exon 5, which results in the insertion of five amino acids, SSMAG, into the protein variant, and which introduces a premature stop codon in exon 6. Aggregation of the PSEN2 variant protein was detected in the hippocampus and cerebral cortex of patients with sporadic AD. The protein variant also was detected in sporadic AD patients, in the frontal lobe of patients with bipolar disorder, and in patients with schizophrenia. The PSEN2 variant is upregulated under hypoxic conditions in cell culture, and a study has shown that the PSEN2 variant influences the conformation of tau protein in human neuroblastoma cells.

**PSEN2 protein**

**Structure**

PSEN2 is located on chromosome 1, and it encodes the PSEN2 protein. PSEN2 is a transmembrane protein with 448 amino acids and a molecular weight of 55 Da. It is predicted to span the lipid bilayer nine times. PSEN2 and PSEN1 are homologous, with a similarity of 67%. The two proteins differ at the N-terminus and at the hydrophilic loop, while the hydrophobic region is highly conserved. PSEN2 is an unstable holoprotein. It undergoes autocatalytic endoproteolysis within the large cytoplasmic loop domain, to form a stable and biologically active heterodimer. In PSEN2, two aspartyl residues—D263 and D366 found in the adjacent transmembrane regions Transmembrane domain (TM)-VI and TM-VII—are the active sites of the γ-secretase complex.

**Location**

PSEN2 has two isoforms. Isoform 1 is found in the placenta, skeletal muscle and heart, while isoform 2, which lacks amino acids 263–296, is found in the brain, heart, placenta, liver, skeletal muscle, and kidney. Presenilin proteins that are localized in neurons reside in the endoplasmic reticulum and Golgi.

**Function**

Presenilin, an aspartyl protease, is a subunit of γ-secretase. γ-Secretase participates in the cleavage of APP, which can produce different lengths of β-amyloid peptide (Aβ). The Aβ42 form aggregates easier than the Aβ40 form. The accumulation of Aβ in the brain is a pathological characteristic of AD. The process of Aβ aggregation is shown in Figure 1. PSEN2 mutation might increase γ-secretase activity. Cell-based studies and mouse models have shown that some PSEN2 mutations cause an increased production of Aβ42, which is a major hallmark in the brains of patients with AD. Presenilin mutations are a major risk factor for AD. Several studies have indicated that AD-related presenilin mutations can alter intracellular calcium signaling, which leads to Aβ aggregation to form brain plaques and neuronal cell death.

γ-Secretase catalyzes the intramembrane cleavage of integral membrane proteins. It plays an important role in intracellular signaling, including Notch signaling and APP processing. In separate studies published in 1996, Vito et al. and Wolozin et al. proposed that PSEN2 is involved in apoptosis. A study demonstrated that wild-type and mutant N141I–PSEN2 trigger p53-dependent apoptosis in HEK293 human cells and in murine neurons. In primary rat cortical neurons, PSEN2, overexpression significantly increased susceptibility to staurosporine-induced apoptosis. PSEN2 mutations can promote apoptosis. Bcl-2 can down regulate pro-apoptotic activities, which are induced by PSEN2. A recent study suggested that overexpression of human mutant PSEN2 induces changes in glucose metabolism, which is accompanied by a decrease in insulin levels.

**PSEN2 mutations**

Mutations in the presenilin genes are the main causes of familial EOAD. Similar to APP, mutant presenilins can enhance Aβ production and contribute to AD development, whereas PSEN2 plays less of a role than PSEN1. An extensive literature search for mutations in PSEN2 was conducted. As
of date, 38 mutations have been reported. The number of mutations identified in \textit{PSEN1} is greater than five times this number.\textsuperscript{31} Two \textit{PSEN2} mutations, Glu126fs and Lys306fs, are frameshift mutations, and the others are nonsynonymous substitutions (Table 1). \textit{PSEN2} mutations are associated with variable penetrance and a wide range in the age of disease onset, from 45 to 88.\textsuperscript{32,33} \textit{PSEN2} mutations are associated with both EOAD and LOAD. Only 17 of the 38 are predicted to be disease-causing mutations (Figure 2). Ten of the mutations are not pathogenic and the others are still unclear. Sixteen mutations are located within transmembrane domains. Cell-based studies suggest that four of these mutations, T122P, N141I, M239I, and M239V, cause an increase in the amount of Aβ peptide.\textsuperscript{34} The mutations T122R, S130L, and M239I were found to alter calcium signaling.\textsuperscript{35–37} Most of these mutations were discovered in European and African populations. Until now, only four missense mutations were described in Asian populations: Asn141Tyr was associated with EOAD in a Chinese Han family;\textsuperscript{37} Gly34Ser was found in a Japanese patient;\textsuperscript{79} and Arg62Cys and Val214Leu were described in the Korean patients.\textsuperscript{76}

**Related diseases**

It was well-known that some mutations in \textit{PSEN2} cause familial AD, while some \textit{PSEN2} mutations are associated with other disorders, including DLB, FTD, breast cancer, DCM, and Parkinson’s disease with dementia (PDD).

**Dementia with Lewy body**

DLB is a progressive degenerative disease, accounting for 10%–20% of all dementias. The core clinical features of DLB are fluctuating cognition, recurrent visual hallucinations, and motor features of Parkinson’s disease.\textsuperscript{40} Lewy bodies, an abnormal aggregation of protein, are found throughout the brain of DLB patients and in patients with other brain disorders, including AD and PDD. In 2008, a \textit{PSEN2} missense mutation, a C-to-T substitution at the second position of codon 85 leading to an alanine to valine substitution in the transcribed protein, was found in a proband with the

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**Figure 1** The process of Aβ aggregation.

**Notes:** Amyloid precursor protein (APP) is a transmembrane protein. APP processing includes non-amyloidogenic and amyloidogenic pathways. Non-amyloidogenic pathway (left): APP is cleaved by α-secretase in the middle of Aβ with production soluble APPα (sAPPα) and C-terminal fragment α (CTFα). Then CTFα is hydrolyzed by γ-secretase to generate APP intracellular domain (AICD). Amyloidogenic pathway (right): APP is cleaved by β-secretase resulting in N-terminal soluble APPβ (sAPPβ) leaving the C-terminal fragment β (CTFβ) which is hydrolyzed by γ-secretase to yield Aβ and AICD. Presenilin, nicastrin, anterior pharynx-defective 1 (APH-1) and presenilin enhancer 2 (PEN-2) are the parts of γ-secretase. \textit{PSEN} mutation might increase γ-secretase activity to cause plaque forming.

**Abbreviations:** AICD, APP intracellular domain; APP, amyloid precursor protein; APH-1, anterior pharynx-defective 1; CTFα, C-terminal fragment α; CTFβ, C-terminal fragment β; sAPP, soluble APP; PEN-2, presenilin enhancer 2.
Table 1  PSEN2 mutations

<table>
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<th>Codon</th>
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<th>Protein domain</th>
<th>Phenotype</th>
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(Continued)
Table 1 (Continued)

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Abbreviations: Aβ, β-amyloid peptide; AD, Alzheimer’s disease; EX, exon; FAD, familial Alzheimer’s disease; DCM, dilated cardiomyopathy; EOAD, early-onset AD; LOAD, late-onset AD; PDD, Parkinson’s disease with dementia; PSEN2, presenilin2.

...clinical phenotype of Lewy body dementia. Neuropathological examination of the proband showed a mass of cortical Lewy bodies and hallmark lesions of AD. In his family, this mutation was identified in six carriers across two generations, with variable clinical presentation. Except for a young family member that was still asymptomatic, all carriers of the A85V mutation developed AD, DLB, or both. None of the patients carried other mutations in AD-related genes. The pathological PSEN1 mutation, A79V, is homologous to the A85V mutation in PSEN2.55 Sequence phylogenetic analysis suggested that the A85 residue is highly conserved. The mutation is located on the N-terminal, cytoplasmic side, adjacent to the TM-I domain that might be critical for the protein function. Overall, it was predicted that the A85V mutation is pathogenic. In all family members with PSEN2 A85V, the genotype of apolipoprotein E (ApoE) was ε3/ε3, which suggests that α-synuclein pathological structures are linked to PSEN2 A85V without affecting the ApoE ε4 allele.52 A PSEN2 mutation, R71W, was reported in a 73-year-old European patient with cognitive impairment and extrapyramidal symptoms, which was likely undiagnosed for DLB. One of the proband’s brothers also carried the R71W mutation and suffered an unspecified type of dementia. The other brother was healthy and did not have a PSEN2 mutation. The R71W mutation was previously identified in AD patients predicted to be possible pathogenic.70 A PSEN2 mutation, R62H, presented in a DLB patient, with no history of neurological diseases, who showed extrapyramidal signs was characterized by a slight left arm rest tremor, bilateral upper limb postural tremor, and bradykinesia on the left side.86 This mutation, located in the N-terminal of PSEN2, is conserved between PSEN1 and PSEN2. Walker et al showed that the R62H mutation did not affect Aβ42 levels or the Aβ42/Aβ40 ratio.34 Guerreiro et al used PolyPhen-2 to show that the R62H variant is likely benign.41 Based on these data, it is highly probably that PSEN2 R62H can be characterized as “not pathogenic”. Since the age of onset in carriers of the R62H mutation is significantly earlier than in affected non-carriers even after correcting for ApoE genotype, the R62H mutation may function as a disease modifier.48

Breast cancer
Breast cancer is the most common malignancy among women in Europe and the US. Two PSEN2 mutations, R62H and R71W, have been identified in patients with breast cancer.
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The mutations are located in the hydrophilic, N-terminal domain. In HEK293 cells, the R62H and R71W mutations did not affect the levels of the PSEN2-CTF and PSEN2-NTF proteolytic products or the Aβ(42)/Aβ(40) ratio, but did influence PSEN2 stability. Full-length PSEN2 degenerated rapidly. In a study using transgenic Caenorhabditis elegans, the R62H and R71W mutations compromised PSEN2 function in Notch signaling.49 PSEN2 has several potential roles in cancer. Deng et al and Wolozin et al reported that PSEN2 has pro-apoptotic activity.27,87 A study also has shown that PSEN2 can also adjust β-catenin levels and act in a p53-dependent mechanism to regulate cell growth.49 In 2013, a study suggested a significant role for γ-secretase in breast cancer.48

Frontotemporal dementia

FTD, a clinical phenotype of frontotemporal lobar degeneration, is the second most common form of early-onset (<65 years) neurodegenerative disease after AD.89 It is mainly characterized by deterioration of behavior, personality, and language abilities.99,100 The prevalence of FTD is between 10% and 30% of all presenile dementia.91–96 FTD has a number of clinical phenotypes and pathological subtypes.97,98 Clinical and molecular overlaps between AD and FTD or FTD-like phenotypes have been reported.99 To date, at least four PSEN2 mutations have been found in FTD patients. In 2010, PSEN2 R62H was found in a 31-year-old patient. The patient’s healthy mother also carried this mutation. The interaction of the H1 MAPT haplotype and the ApoE ε2 allele might function as a protective modifier against FTD, while the H1 MAPT haplotype unaccompanied by the ApoE ε2 might be a risk enhancer for FTD.53,100 These possibilities imply that modifier, suppressor, and enhancer effects of multiple genes may be crucial for genetic analysis.

Dilated cardiomyopathy

DCM is a heart muscle disease in which the heart becomes enlarged and cannot pump blood efficiently. DCM usually leads to heart failure. The causative factor for DCM has not been determined, but DCM in families is genetically linked. In 2006, the PSEN2 S130L mutation was identified in two Caucasian families. It is highly conserved. Several family members with this mutation suffered DCM and heart failure.36 Presenilin is expressed in multiple tissues, including in the heart, and it is required for cardiac development.101–104 Calcium signaling was altered in cultured skin fibroblasts

Figure 2 Missense mutations in PSEN2 and their pathogenicity.
Abbreviations: SNP, single nucleotide polymorphism; EX, exon.
from carriers of the mutation. The \textit{PSEN1} D333G also was identified in a DCM patient. Compared to the phenotypes seen in carriers of \textit{PSEN1} D333G, the phenotypes are milder in carriers of \textit{PSEN2} S130L, and \textit{PSEN2} S130L is not associated with heart failure as often. Currently, it is not clear whether γ-secretase activity is related to DCM. The Notch family of proteins is one of the major transcriptional regulators of cardiac growth and development.\textsuperscript{105} Disordered Notch signaling is associated with valvular abnormalities, syndromic cardiovascular disease, congenital heart disease, and myocyte dysfunction.\textsuperscript{106} \textit{PSEN2} knockout (PS2KO) mice grow normally without cardiac hypertrophy and fibrosis, while cardiac contractility improved.\textsuperscript{107} \textit{PSEN2} plays an important role in cardiac systolic function by modulating Ca\textsuperscript{2+} signaling.

**Parkinson disease with dementia**

Parkinson’s disease (PD) was first described by James Parkinson in 1817. PD is a chronic, progressive, neurological disease that results from the destruction of nerve cells in the basal ganglia. The disease mainly affects movement, but as the neurological damage progresses, the disease often affects mental functions. PDD is an impairment in thinking and reasoning that eventually affects many people with PD. A 77-year-old carrier of \textit{PSEN2} V191E showed the PDD phenotype characterized by cognitive decline, visual hallucinations, and confusion during the final years of the PD. This \textit{PSEN2} mutation is located at a highly conserved amino acid residue in the protein. In a study by Bram Meeus, the V191E mutation did not exist in more than 1,200 control individuals, so he predicted that V191E is a damaging mutation.\textsuperscript{79} A \textit{PSEN2} R163H variant has been reported in a Swedish PD family in who were also found a de novo α-synuclein A53T mutation. The proband’s mother also carried the mutation \textit{PSEN2} R163H, but she was healthy. Nevertheless, this mutation cannot be excluded with certainty as a cause of PD when in combination with α-synuclein.\textsuperscript{90} \textit{PSEN2} S130L was identified in a patient with of LOAD, and his two siblings were diagnosed with PD. Unfortunately, the genetic results from the siblings are not available. The S130L mutation was also detected in the proband’s two unaffected children, but the segregation of the disease could not be determined. The correlation between PD and AD is not clear.

**Conclusion**

This review described mutations in \textit{PSEN2} from diverse disorders. Mutations in \textit{PSEN2} were shown to be a rare cause of familial AD. Pathogenic mutations in the \textit{PSEN1}, \textit{PSEN2}, and \textit{APP} gene account for 18%–50% of familial EOAD cases with autosomal dominant pattern of inheritance.\textsuperscript{108} \textit{PSEN} genetic testing results could provide genetic counseling for patient’s family members. There is a considerable interest in the application of this genetic information in medical practice through genetic testing and counseling. \textit{PSEN2} mutations are involved in not only AD but also in other disorders, including FTD, DLB, PDD, breast cancer, and DCM. Why are \textit{PSEN2} mutations found in multiple diseases? Are these diseases related? Until now, the answer to this question has been unclear. There are several possible reasons that \textit{PSEN} is associated with multiple diseases. \textit{PSEN2} is a transmembrane protein that is a component of γ-secretase intramembrane protease. γ-Secretase is required to process several types of integral membrane proteins, and is involved in different signaling pathways. Mutations in \textit{PSEN2} may disrupt the normal pathways and lead to different disorders. Thus, it can be hypothesized that these disorders might share underlying genetic factors. On the other hand, different neurodegenerative diseases show slightly different behavioral, language, and motor symptoms. Sometimes it is difficult to distinguish them clearly by clinical diagnosis. Many patients with both PDD and DLB have hallmark changes in the brain, including plaques and tangles that are associated with AD. These observations suggest that there may be a common pathogenetic mechanism in the formation of aggregated proteins. Therefore, mutations in \textit{PSEN2} might play a role in Aβ, α-synuclein, and tau aggregation.

Overall, genetic studies have already indicated that \textit{PSEN2} may affect people with FTD, PDD, LBD, breast cancer, and DCM. How presenilin 2 is implicated in the pathogenesis of these diseases is still unclear. This question needs to be further explored.

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