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REVIEW ARTICLE

A Review on the Role of Presenilin in Alzheimer's Disease

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ABSTRACT:
Alzheimer's disease (AD) is the most common form of dementia. It characterized by the presence of numerous senile plaques and neurofibrillary tangles in the cerebral cortex and hippocampus of affected individuals. 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 review of studies describing the mutations identified in PSEN1 and PSEN2. This article brings about the information pertaining to the role of presenilin and its derivatives in Alzheimer's disease.

KEYWORDS: Alzheimer's disease, Amyloid precursor protein, Mutation, presenilin 1, presenilin 2.

INTRODUCTION:
Alzheimer's disease (AD) is a complex and heterogeneous neurodegenerative disorder. Various genetic and environmental agents and gene interactions may be implied in the disease's occurrence and progression classified as either early onset (under 65 years of age), or late onset (over 65 years of age). Only symptomatic treatment is currently available; however, there is a legitimate hope for a cure thanks to the tremendous progress that is being made in understanding the molecular pathogenesis of the disease. Experiments have been performed with mono- and dizygotic twins to estimate the role of genetics in AD, the environmental influences, and the disease heritability. Variation in age of onset, neuropathological patterns, and disease duration may be possibly due to genetic–environmental interactions.[1,4] As a polygenic disorder, several additional factors might be potential risk factors for AD. Many single-nucleotide polymorphisms (SNPs) have been identified and affirmed to be linked with AD.

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The bulk of recent subjects in the genetics of AD has focused on the identification of novel risk-factor genes and mutations.[2,5,6] Three main factors are involved in early onset AD: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Presenilin mutations are the primary case of familial Alzheimer disease. From a genetic point of view, these mutations seem to result in a gain of toxic function.

STRUCTURE AND FUNCTION OF PRESENILIN:
The structures of *PSEN1* and *PSEN2* are similar, with a homology of 67%. Both of them contain 12 exons with ten coding exons (exons 3–12) for a protein of ~450 amino acids. Presenilin 1 (PS1) and presenilin 2 (PS2) proteins are transmembrane (TM) proteins with at least seven TM domains.[7]

The role of presenilin was that two transmembrane aspartate (257 and 385) residues in PS1 are critical in gamma secretase activity. 20 Most AD risk-factor mutations have been detected in PSEN1 (approximately 30%–70% of early onset FAD), which is situated on chromosome 14. PSEN2, on chromosome 1, is another risk-factor gene for AD.[8]

Presenilin possesses a 9 transmembrane domain topology, with an extracellular C- Terminus and

cystosolic N- terminus. Most cases of Alzheimer's disease are not inherited. Nevertheless, in that respect is a minor subset of instances that have an earlier age of onset and cause a strong genetic component. In patients suffering from Alzheimer's disease (autosomal dominant hereditary), variations in the presenilin proteins (PSEN1; PSEN2) or the amyloid precursor protein (APP) can be put upwards. The majority of these cases carries mutant presenilin genes. An important part of the disease process in Alzheimer's disease is the accumulation of Amyloid beta (Aβ) protein.

MUTATION:

APP mutations result in only a modest proportion of autosomal dominant inherited types of AD. The first *PS1* mutation associated with FAD was reported in 1995. Nearly all of the reported PS1 mutations are missense and give raise to the exchange of a single amino acid. A Mutation in the intron was also set up to be able to produce AD.[9,10,11]

The gene for presenilin 2 (PS2) was first identified on chromosome 1 in the public nucleotide sequence database, and suffers an overall 62% homology to PS1.[12,13,14,15]

Biochemical studies have shown that PS1 and PS2 both have eight membranes spanning segments with a large hydrophilic loop between the transmembrane domains 6 and 7, and the N-terminus and C-terminal both face the cytoplasm. This unique structure confers their capacity to interact with other cytoplasmic proteins. Loss of presenilin function results in diminished **Aβ** production.

To date, more than 200 mutations have been described in PSEN1 throughout the universe, but mutations in PSEN2 are extremely uncommon. Less than 40 mutations in PSEN2 have been identified.Patients with PSEN1 mutations might develop AD symptoms in their 40s or early 50s, with a few cases occurring in persons in their late 30s and early 60s. Several missense mutations in PSEN1 can increase the production of Abeta 42 and 40. In an alternative mechanism, the levels of Abeta 42 and Abeta 40 might be increased and decreased, respectively.[16]

Mutations near the cleavage site of alpha secretase (Glu693Lys, Glu693Gly, Glu693del, Asp694Asn) might change the processing of APP, in enhancing the proteolytic resistance of Abeta peptide.[17,18]

So far, more than 150 familial AD-causing mutations in PSEN1 has been identified, approximately 10 additional mutations have been found in the homologous gene PSEN2.(http://www.molgen.ua.ac.be/ADMutations).[19]

Most mutations in PSEN1 are simple missense mutations that result in single amino-acid substitutions in presenilin 1. Some are more complex, for instance, small deletions, insertions or splice mutations. PSEN1 mutations could be involved in forms of frontotemporal Dementia without the involvement of Aβ.

Three genes have considered the main risk factors for EOAD: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2. Variations in these factors might result in alteration of amyloid beta (Abeta) production (both Abeta 40 and Abeta 42), contributing to apoptosis of the neurons and dementia.[20,21,22,23] Presenilin 1 (PS1) and presenilin 2 (PS2) proteins are transmembrane (TM) proteins with at least seven TM domains.[24] The function of presenilins was first described by Wolfe et al, who proposed that two transmembrane aspartate (257 and 385) residues in PS1 are critical in gamma secretase activity.[25]

Almost all of the reported *PS1* mutations are missense and give rise to the substitution of a single amino acid. So far, only two splicing defect mutations have been reported; these changes the topography of the protein in membranes. In addition, the mutations are most frequently observed in exon 5 (28 mutations), exon 7 (23 mutations), and exon 8 (20 mutations). A mutation in the intron was also found to be able to produce AD.83 Of the 120 *PS1* mutations reported, the majority was only found in a single AD family. The most frequently observed is the AD-associated *PS1* mutation at codon 206 (Gly206Ala)

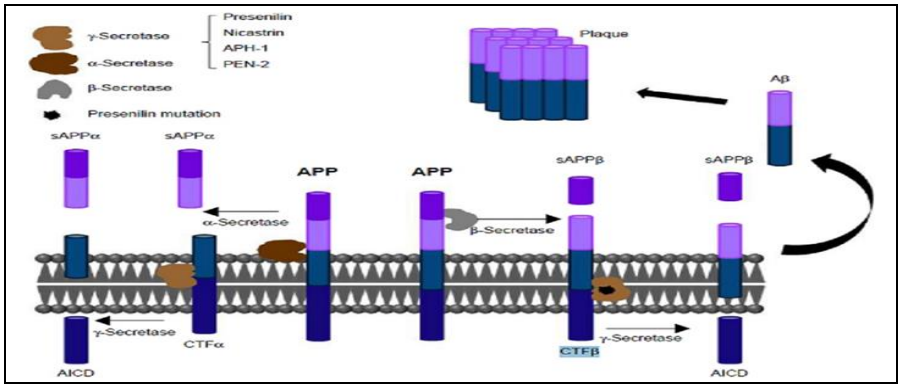

Fig 1: The process of Aβ aggregation.

PRESENILIN 2:

Presenilin, an aspartyl protease, is a subunit of γ-secretase. γ-Secretase participates in the cleavage of APP, which can create 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.[26]several studies have indicated that AD-related presenilin mutations can alter intracellular calcium signalling, which leads to Aβ aggregation to form brain plaques and neuronal cell death. [27,28]PSEN2 mutations are associated with both EOAD and LOAD.

CONCLUSION:

AD is the most common form of senile dementia, but it can sometimes be difficult to distinguish heterogeneous neurodegenerative disorders. Finding the potential genes involved in AD progression is an essential step in molecular diagnosis. Genetic testing should be important to understand the mechanisms and pathways leading to neurodegeneration and disease symptoms. Genetic analysis can improve the differential diagnosis of neurodegenerative dementias. Presenilin 1 and presenelin 2 mutations causing the major onset of Alzheimer's disease. Like there is definitely a need in blocking presenlin 1 and presenilin 2 in order to reduce the impact of disease.

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