Alzheimer's Disease Genetic Mutations: Mini Review

Abstract
Alzheimer's disease is poorly understood and continuously evolving with research. There have been many genetic mutations linked to Alzheimer's disease. Amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have been identified as causative gene mutations with early onset of Alzheimer's disease. Another genetic factor of AD is apolipoprotein E (APOE) which has been associated with the more common form of AD - late onset Alzheimer's disease. Understanding the genetic involvement of Alzheimer's disease may lead us to early detection, prevention, and ultimately definitive treatment or even a cure. In conclusion, the genetic factors of Alzheimer's disease.

Keywords: Alzheimer's disease; Amyloid precursor protein; Presenilin 1 (PSEN1); Presenilin 2 (PSEN2); Apolipoprotein E (APOE); Genetics

Introduction
Alzheimer's disease is one of the least understood brain disorders. The genetic association of Alzheimer's disease (AD) is an area that attracts the interest of neuroscientists since it is similar to other neurological illnesses but quite a complex disorder. It is considered to be a genetically dichotomous disease exhibiting two currently documented forms known as early onset familial cases that usually characterized by Mendelian inheritance and late onset after age 65, with no consistent mode of transmission [1]. Alzheimer's disease is an autosomal dominant inheritance disorder. Most families with AD typically develop symptoms between the ages of 30 to 60 years old. The greatest risk factor of Alzheimer's is age. Genetic predisposition for AD has been in research. There have been many genetic mutations linked to Alzheimer's disease.

Discussion
Amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have been identified as causative gene mutations with early onset of Alzheimer's disease [2-4]. APP gene is located on chromosome 21q and encodes the protein product [5]. The APP (amyloid precursor protein) forms into the Aβ (β-amyloid) peptide that is neurotoxic in the brain. It is the accumulation of Aβ in the brain along with cleaved forms of microtubule protein tau that lead to Alzheimer's dementia. The exact mechanism to why Aβ accumulates in the brains of elderly is not completely understood at this time [6]. More than 30 mutations of the APP gene have been identified in the association with AD and account for approximately 10-15% of early onset familial Alzheimer's Disease. The function of APP is still being researched but it is believed to be an important player in the synaptic transmission.

Roughly half of early-onset AD pedigrees have been associated with mutations in PSEN1 and PSEN2, primarily in PS1. Presenilin 1 gene is located on chromosome 14q and encodes the protein product [7]. More than 150 PSEN1 mutations have been identified with early onset of AD. Accounting for 50% of early onset familial AD, mutations fully penetrate and associate with earlier median age of onset compared to APP and PSEN2. PSEN1 has several different functions including regulation of intracellular calcium signaling, cell cycle and cell death, trafficking of membrane proteins, regulation of Beta-catenin stability, and Notch signalling. Small deletions and insertions have been described and most mutations of PSEN1 are missense mutations [8].

Presenilin 2 gene is located on chromosome 1q and encodes the protein product PSEN2 [9]. PSEN2 is the rarest form of AD, mutations fully penetrate and associate with earlier median age of onset compared to APP and PSEN2. PSEN2 is also thought to be estimated 95% penetrant whereas APP and PSEN1 are thought to be fully penetrant [10]. PSEN2 are thought to act in the part of enhancing the apoptotic activity which leads to neurodegeneration [11]. PSEN2 mutations alter the cleavage activity of PSEN2 mutations alter the cleavage activity of y-secretase and increase the ratio of Aβ 42 to Aβ40 which is similar to PSEN1 mutations.

Another genetic factor of AD is apolipoprotein E (APOE) which has been associated with the more common form of AD -late onset Alzheimer's disease [12]. The APOE gene or apolipoprotein E has 3 common alleles in humans, which are numbered 2,3, and 4. The APOE-4 allele is present in 20% to 30% of the general population but in 45% to 60% of patients with AD; APOE-4/4 homozygotes constitute approximately 2% to 3% of the general population but 12% to 15% of patients with AD. Many APOE-4/4
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Both anomalies affect the hippocampus it is especially difficult to discern between the two pathologies, except that LBD manifests a greater EEG wave deceleration [16].

Alzheimer’s disease continues as one of the most challenging disorders of the modern era and is considered a public health crisis. Alzheimer’s disease effects on patients are devastating. The burden on a caregiver is dreadful, and the cost on the society is daunting. Understanding the genetic involvement of Alzheimer’s disease may lead us to early detection, prevention, and ultimately definitive treatment or even a cure. In conclusion, the genetic factors of Alzheimer’s disease remains poorly understood despite many advances within genetic testing. Further research initiatives are needed to revolutionize our understanding of the human mind and discover new ways to treat, prevent, and cure brain disorders such as Alzheimer’s disease.

References
