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The Genes Associate with Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a common chronic neurological disease. In an aging society, the incidence rate is increasing year by year and remains high. Due to the decline of intelligence and cognition in patients, it is a heavy burden to the family and society. However, its pathological mechanism is not fully explained, and there is a great deal of controversy recently. Previous studies have shown that AD is characterized by the accumulation of neural plaques and neurofibrillary tangles caused by abnormal accumulation of Aβ protein. There are also studies showing that the dysfunction of cholinergic neurons may lead to its occurrence and development. Namely, degeneration of cholinergic neurons occurs in AD and leads to alternating cognitive function and memory loss. Current treatments for AD are very limited. This situation has led to the research focus on the risk factors for the occurrence of the disease. Age, genetics and environmental factors play different roles in the development of AD. Genetic inheritance may be the basis of individual susceptibility. This article briefly introduces genetic factors and specific genes associated with AD in order to further our understanding of how this disease occurs.

Key words: Alzheimer's disease, gene, heredity, A β protein.

1. Introduction

Alzheimer's disease, found by German doctor Alois Alzheimer, is one of the most common reason of the loss of memory and conscious. It is defined as the progressive chronic disease with obvious neurodegenerative property. The character of Alzheimer's disease (AD) is aggregation of neurotic plaques and neurofibrillary tangles caused by the amyloid beta protein accumulating abnormally in brain structures including neocortical structures and medial temporal lobe. AD's typical symptoms is neuropsychological test-confirmed dementia, the continuous process of memory loss, and speech and movement disorders. The biomarkers of it are brain amyloids founded in CSF through PET, and neuronal injury like cerebrospinal fluid tau, fluorodeoxyglucose (FDG) for metabolic activity which is found through MRI [1]. The pathogenesis of it is still not fully established, but there are three hypotheses that are relatively widely accepted. One hypothesis is about the amyloid protein. It is widely accepted that the major factor that causes AD (AD) is considered as the production and aggregation of β-amyloid peptide (Aβ). The amyloid β protein is a kind of 3943 amino acid peptides that consists of the transmembrane region and extracellular region of the amyloid precursor protein (APP) [2]. Although the function of amyloid precursor protein is not defined clearly, indirect evidence supports that the amyloid precursor proteins are involved in mediation of neuronal cells' growth. The amyloid precursor

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protein will be cleaved sequentially by two endonuclease bounded by membrane such as active β-and γ-secretases [3]. In the first step, the β-secretase will cut amyloid precursor protein to get the big secretory derivative sAPPβ. The 99-amino acid fragment bounded by membrance (CTFβ, starting from the N-terminal aspartyl residue of Aβ) and is then quickly cut by γ-secretase to yield amyloid β protein. The cleavage of γ-secretase is somewhat uncertain, give rise to the C-terminal heterogeneity of the product peptide group [4, 5]. Thus, a variety of Aβ species exist, but the species ending in position 40 (Aβ40) have the most abundance (~80-90%), followed by 42 (Aβ42, ~5-10%) [4]. The Aβ, which is a little bit longer, especially Aβ42 and 43, is more fibrillary and hydrophobic, which could be considered as a seed for future accumulation amyloid beta proteins. Although the existence of deposition of amyloid beta protein accumulate in the brain is believed as a pathological characteristic of AD, the specific role of amyloid beta protein plays in the pathological symptoms of AD's development and the death of neurons are still not be understood very well. However, a variety of studies demonstrate that in aggregates state, amyloid beta protein probably have the toxic properties [6,7]. The aggregated amyloid beta proteins are considered may have the negative influence on transmitters or synaptic markers between neurons, and even attribute to the neurons death by inducing apoptosis [4,5,7]. These factors will finally lead to the loss of cognition. Another hypothesis related to the cause of AD is about the cholinergic. This hypothesis claims that AD caused by the deficiency of acetylcholine. This insufficiency is called deficits of presynaptic and neocortical cholinergic and is believed that it can have association with enzyme choline acetyltransferase, the enzyme responsible for synthesis acetylcholine. In the human brain, acetylcholine is closely related to a variety of physiological processes, including storing memory, learning , receiving sensory information, paying attention and other key functions [8]. Some study confirmed that degeneration of cholinergic neurons occur in AD and lead to alternating cognitive function and memory loss. The third well-known hypothesis is the Tua protein hypothesis. The hypothesis advocates that the protein named tau is an important factor that lead to AD has long been supported by observing the aggregating amyloid plaques and has low correlation with neuronal loss [8]. A neurotoxic mechanism has been introduced due to the dispossession of tau which is stabilized by microtubule and give rise to the deterioration of cytoskeletal. However, there is no agreement on whether the hyperphosphorylation process of tau happens prior or after the production of the plague of harmful helical filament. Moreover, evidence for the Tau hypothesis has the relationship with the existence of some disorders such as tauopathies, in which tau proteins also misfolds [8]. There are multiple risk factors such as age, genetic and environmental factors. Among them, environmental factors included heavy metals, trace metals, etc. [8]. One of the most important factors is the genes inheritance since it could screen people with high risk in advance, and can also help develop gene therapy drugs that target specific genes. The inheritable factors and specific genes correlated with AD will be discussed detailed in the following essay.

2. APOE gene and its association with AD

2.1. Introduce to APOE gene and it's function

APOE gene has 4 variants. The APOE gene is essential for the body's processing of cholesterol and triglycerides and instructs the formation of apolipoprotein E which forms lipoproteins. These lipoproteins called apoE protein are responsible for carrying cholesterol and fats through the bloodstream. apoE protein of human have in three types different in substituents of amino acid at 112 ad 158 positions, have the influence in the risk of getting disease of carriers. The relative frequencies of 4 allele such as ε2, ε3, and ε4 in the world population were approximately 7%, 78% and 14%, respectively. ApoE3 has Cys at position 112 and Arg at position 158, while apoE2 and apoE4 has Cys and Arg at position 6, respectively. ApoE3, the most common ApoE3 isoform, play an important role in metabolizing the lipoprotein normally [9] . At the same time, apoE2 and ApoE3, which have less abundance, are related to metabolic abnormalities. To be more specific, APOE3 is typically the "best" variation of the gene and is most effective in removing fat and cholesterol from the bloodstream by synthesis the lipoprotein isoform. In contrast, APOE2 and APOE 4 are the variations of the gene that

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are less successful at removing these fats and cholesterol from the bloodstream due to the lipoprotein isoform they are responsible to produce. This less effective capability to remove fat and cholesterol from the bloodstream leads to a greater risk of heart disease in individuals with one or more copies of the APOE2 or APOE4 gene due to a greater concentration of fat and cholesterol within the blood which builds along the walls of the arteries. Similarly, there are various evidence shows that individuals with one or more copies of the APOE4 gene more chance of developing AD, which suggests there is association between APOE gene and AD.

2.2. relationship between APOE gene and AD

APOE4(one of the variants) has a special affinity with amyloid peptide, which contributes to the production of damaging plaques in the cell and result in AD. The apolipoprotein E gene controls the synthesis of apolipoprotein E. ApoE protein promotes the aggregation of Aβ protein. Studies have shown that it influence the accumulation of Aβ and lead to CAA, which are markers of AD brain amyloidosis, and the carriers are slightly to have Aβ plaques. Among people 50 to 59 years of age, 40.7% of apolipoprotein Eε4 carriers had Aβ accumulation, while only 8.2% of non-apolipoprotein Eε4 carriers had abnormal protein accumulation [9]. Among all Alzheimer's patients who show signs of abnormal protein accumulation, apoEε4 carriers are more common than those without abnormal amyloid accumulation. This phenomenon was more common in apoE4 carriers and less common in apoE2 carriers. It has been speculated that apoE may be A protein that can bind Aβ. ApoE can induce pathological changes in the structure of Aβ. Compared with those without the 4 allele, those with one 4 allele have higher risk by 2-3 times, while those with two 4 alleles have an approximately 12-fold higher risk. Apoeε4 is linked with an increased prevalence of the disease and early onset. In ε4 homozygotes 7, 10 and 20, the incidence and mean age of AD were 98% and 68 years, respectively. The incidence of AD was 47% and 76 years in the carriers, and 20% and 84 years in non-carriers, respectively. These results suggest that apoEε4 carriers have an early incidence for developing the disease. It is also shown that the relative opportunities to carry one isoform of APOE gene is related to ethnic groups. The frequency to carry an E4 copy is about 15% for Asians and more than 50% for New Guineans [10]. The presence of the APOE4 genes could reflect traditional diets in different ethnic groups. For instance, the APOE4 genes, which are found most frequently in New Guineans, appear to be related to their traditional low fat diets including taro, sugar cane, and possums' lean meat.

3. APP gene

3.1. Introduction to APP gene

The APP, located on chromosome 21, is responsible for making amyloid precursor protein (APP protein), which is an integral membrane protein [1]. This protein is usually expressed in a variety of tissues, especially in the synapses. This is due to the fact that APP proteins can act as cell surface receptors and thus participate in synaptic formation, neuroplasticity, antimicrobial activity and iron export [1]. Its amyloid fibrillary form is the main resourse of Aβ plaques. It can be degraded by secretase to obtain Aβ peptide fragments.

3.2. Relationship between APP gene and AD

The by-products of APP protein can be degraded through γ-secretase to Aβ peptide extracellular. The aggregation of Aβ protein in neurons is considered a hallmark of the disease. Due to the different cleavage sites of γ-secretase, APP protein can produce different C-terminal amyloid β peptides, such as Aβ40 and Aβ42 [4]. Under normal physiological conditions, Aβ40 has A variety of amyloid variants, among which Aβ42 accounts for only 10% of the total Aβ. However, mutations of it resulted in increased production of Aβ42, which is considered A harmful polypeptide because it more readily forms fibers and promotes Aβ aggregation, leading to AD. More than 30 dominant mutations of the gene have been found and are linked with about 15% of early onset AD cases. Among them, five variants such as

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APPSW, APPK670N, M671L APPLON and APPV717I were considered to be related to the increase of Amyloid beta protein and important risk factors to develop the disease [11].

4. PSEN1 gene

4.1. Introduction of PSEN1 gene

PSEN1 gene is the gene that code for presenilin-1 protein. It is vital proteins of the γ-secretase complex, and is thought to make sense in the production of Aβ from APP. To stabilize and active the γ-secretase complex, it is necessary to have the proteins including anterior pharyngeal defect 1 (APH-1), PSEN1, presenilin enhancer, and Nicastrin (Nct) [3]. Under the hydrophobic condition due to the membrane phospholipid bilayer, the secretase complex can cut various transmembrane proteins, such as APP and Notch.

In mouse model with PSEN1 knockout, gene loss was restricted to the postnatal forebrain, and mice with the knockout gene were found to exhibit less serious cognitive impairment in long-term continuous memory about the space [3]. These results imply the impact of presenilin on the cognitive memory. Furthermore, knock-in mice, which has the endogenous mouse PSEN1 missense mutations, will tend to show soaring level of Aβ42 and have bad performance on tests identifying the object. These suggest that mutations of it play a role in Aβ production.

4.2. Relationship of PSEN 1 gene and AD

The mutation of PSEN 1 gene will lead to the reduce of the function of γ -secretase and finally lead to the accumulation of A β 42 protein. The wrong expression or translation in PSEN1 result in early onset age of the disease. However, large variation in the age of onset yet was found. The average age of onset of other AD cases that have the association with PSEN1 usually older than 58. Psen1-associated AD is an autosomal dominant disease. The disease often has neurodegenerative symptoms such as loss of consciousness and loss of limb control, and Alzheimer's patients with the PSEN1 gene also include other atypical AD symptoms such as limb spasms. The clinical diagnosis of AD associated with PSEN1 gene is usually confirmed by measuring amyloid plaques and nerve degeneration in other brain regions. For example, one family with PSEN1 was found to have family members who experienced memory loss, limb cramps and seizures. The diagnosis of AD was confirmed by neuropathologic examination of these family members. In addition, a PSEN1 mutation (I143M), thought to occur in the vicinity of a second transmembrane protein region, was identified with onset in the early 50s and persisted 6 to 7 years [3]. The patient's neurons were detected to contain plaques and neurofibrillary tangles caused by abnormal accumulation of Aβ protein. This particular lesion extends even to the brain stem. This is enough to show that the mutation of PSEN gene has a strong correlation with the onset of AD

5. PSEN2 gene

5.1. Introduce to PSEN2 gene

The PSEN2 gene has been found on chromosome 1. There are 12 exons in PSEN 2which could be organize 10 translated exons encoding a peptide contains 448 amino acids [3,5]. It consisted of nine transmembrane domains and a small hole between the 6th and 7th transmembrane proteins. PSEN2 also shows alternative splicing, which is specific to relevant tissue. Similar to the presenilin 1, presenilin 2 is also made by a typical γ-secretase [3,8].

5.2. Relationship to AD

The expression of PSEN2 could be found in various tissues such as human's brain, mainly in neurons. This shows that PSEN2-related mutations have the ability to increase the ratio between two type pf amyloid beta proteins which is Aβ42 and Aβ40 reflected in the experiments conducts on both mice and human. It is suggested that presenilin protein could alter how APP is dissected by γ-secretase. At sites of γ-secretases, the differential of Amyloid precursor protein is related to particular presenilin mutations.

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For instance, the mutation that is called PSEN1-L166P leads to reduced Aβ production, while the mutation named PSEN1-G384A prominently raises the level of Aβ42 [1]. In contrast, Aβ producers of PSEN2 appear to be less efficient than PSEN1. It is not clear about the biological and functional importance of the variants. However, it appears that differential expression of it may resulted alternative regulation of APP proteolytic. To be more specific, wrong PSEN2 transcripts has the possibility to make an increment in the rate of Aβ peptide production. In the contrast, the isoforms of PSEN1 do not have the exons 3, 4, and 8 shows a little or even no influence on the production of Aβ.

5.3. Differences between the effects of PSEN2 and PSEN 1 on AD

In general, people with PSEN1 gene develop AD at an older age than those with PSEN2 gene. To be more specific, compared to the PSEN1 gene, mutations of PSEN2 are a rare cause of early-onset familial AD, especially in Caucasian ethnic group [8]. The family clinical characteristics impacted by PSEN2 are likely to be different from those affected by PSEN1, since these family members typically have older onset age, usually is 45 to 88 years, than other PSEN1 family members .On the contrary, the age of onset of PSEN2-affected members of the same family does not follow a strict pattern [8]. Missense mutations happen on the PSEN2 gene may have lower chance to be expressed in offspring than on the PSEN1 gene. It is also could be medicated by other genes or environmental factors [8, 3]. Furthermore, compared with PSEN1 mutation, PSEN2 mutation is a rare cause of familial AD. PSEN2 mutations been found in 6 families, whereas PSEN1 were found in 390 families. Until now, 14 PSEN2 mutations have been reported.

6. Conclusion

Although the specific gene causing the disease have not been determined yet, there are at least four important genes that has been found involve in the development of it. The discovery of several genes involved in the development of AD has partially revealed the pathogenesis of AD and greatly improved the possibility of developing effective drugs against AD. All these discoveries and accomplishments are due to the development of genetic technology which enhances a better understanding of the function of genes related to chronic diseases with complex pathogenesis like AD. It could be believed that with the potential development of science and technology, more genes associated to AD will be found. Thus, it is reasonable to believe that AD can be avoided and controlled as much as possible in the future through genetic testing and gene targeted drug.

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