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Review Article

Genetic of Alzheimer's Disease: A Narrative Review Article

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Abstract

Background: Alzheimer's disease (AD) is one of the most common problems for old peoples. Etiology of AD is not clear, but genetic factors play a major role in determining a person's risk to develop AD. Twin and family studies confirm that AD has a genetic basis.AD genetics has been split into two broad categories: early-onset and late-onset. EO-AD cases are inherited in an autosomal dominant pattern. In this form, dominant mutations in genes like APP, PSEN-1 and PSEN-2 associated with AD. This study aimed to consider the role of genetic in AD.

Method: At the first, most of the references in relation with genetic basis of AD searched from the following websites: PubMed, Science direct, Wiley & Sons (1995-2014). Then, the most common genes and their affects described briefly.

Results: Aging is the most obvious risk factor for developing AD. There is a genetic basis for AD, of course this relation is not complete but it is significant.

Conclusion: More than thousand genes studied in relation with Alzheimer's disease. Against the improvements in understanding different aspects of AD, the accurate genetic foundation of AD remain unclear.

Keywords: Alzheimer's disease (AD), Early-onset type (EOAD), Late-onset type (LOAD), Genetic factors

Introduction

Several factors lead to dementia. Alzheimer's disease (AD) is the most common form of dementia (1). AD is the common form of neurodegenerative disease and the sixth leading cause of death in the elderly (2). AD includes two thirds of all dementia (3, 4). AD is a progressive and an age dependent disease (prevalence of AD increase with advancing age) that leads to the irreversible loss of neurons, particularly in the cortex and hippocampus (5). The clinical factors present progressive impairment in memory, judgment, decision making, orientation to physical surroundings, and language.

AD affects about 15 million people around the world and by 2040. It is expected to rise to 80 million (6). About 10 percent of all people above 65 years and 50 percent above 85 years of age suffer from AD (7). Evaluation of the prevalence of AD differs according to the diagnostic criteria, the age of the population surveyed, and other factors like; geography and ethnicity (8, 9). Excluding persons with clinically questionable dementia, Alzheimer's disease consists 1 percent among those 65 to 69 years of age. In addition, prevalence increases with age to 40 - 50 percent among persons 95 years of age and over (8). The mean age at the onset of dementia is around 80 yr (3). All findings indicate that AD increases with age and it progresses more differently in different cases.

AD is a complex disease caused by a combination of age, genetic, and environmental factors. These factors trigger or increase the risk of developing

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AD (10). There is not a clear casual factor for AD. The pathological factors of AD are; the existence of dense intraneuronal neurofibrillary tangles (composed of hyperphosporylated Tau protein) and extracellular amyloid plaques. Epidemiological researches show that increasing age and a positive family history of dementia are the definite risk factors for AD (7). Having an AD affected mother causes a greater risk than having an AD affected father (11). Women are at greater risk of developing AD and this has been correlated to postmenopausal estrogen decline (12). Cardiovascular disease patients and individuals with history of head injury show higher AD risk than normal controls. As it above described, there are many risk factors and no one is sufficient and enough. A family history of AD in the first degree relatives leads to a positive correlation with a fourfold increase in risk in developing the Alzheimer's disease. It stated that there is a genetic basis in AD pathogenesis (13). The risk of AD increases with an affected first degree relatives (7).

Numerous genes that affect the risk of developing dementia have been identified and the biological systems of the disease are now beginning to be understood. Historically, AD genetics has been divided into two categories. First, rare autosomal dominant forms of the disease, typically of Early-Onset AD (EOAD) (< 65 years); and second, the more common form of Late - Onset AD (LOAD). LOAD as the most common form of AD (90percent) in the population occurs individually and is initiated late in life (14). Therefore, this study aimed to consider the considerable genes that affect Alzheimer's disease.

Methods

At first, most of the researches about "genes in AD" were searched from the following websites: PubMed, Science direct, Wiley & sons (1195-2014). Then, according to the existing researches, AD was divided into two parts: Early onset AD and late onset AD. Finally the genes based on each category were described.

Results

Early Onset Alzheimer Disease (EOAD)

EOAD only accounts for less than 10% of all people with AD, but clear genetic foundations have been shown to cause EOAD. In other word, there is a clear genetic ground for EOAD. According to the previous studies, associated genes with EOAD introduced separately:

Amyloid precursor protein (APP)

Down syndrome patients develop the clinical and pathological factors of AD when they live over 30 years then, chromosome 21 as a risk factor of AD is more investigated (14). The code of gene for the amyloid β precursor protein (βAPP) is localized on chromosome 21 in the region 21q11.2-q213 (15). This discovery helped researchers established association between APP gene and AD. The genes causing EOAD are shown in Table 1.

Table 1: Genes causing Mendelian Forms of AD

Gene	Protein	Location	Mutations	Molecular effects/ pathogenic relevence
APP	Amyloid β-protein precursor	21q21	32	Increase in Aβ production or Aβ42/Aβ40 ratio
PSEN1	Presenilin 1	14q24	182	Increase in Aβ42/Aβ40 ratio
PSEN2	Presenilin 2	1q31	14	Increase in Aβ42/Aβ40 ratio

Both APP and Aβ are normal neuronal protein products. Aβ is produced by the sequential proteolytic activities known as γ-secretase and β-secretase. β-Secretase is known as β-site APP-cleaving enzyme1 (16). The γ-secretase function seems to originate from a transmembrane protein complex not only a single enzyme (17). Following β-secretase cleavage of APP, the function of γ-

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secretase produces the Aβ peptide that normally ranges from 38 to 43 amino acids in length. α-secretase as a third enzyme, is involved in normal APP processing. The cleavage local for α-secretase lies within the Aβ sequence and leads to non-amyloidogenic products.

All determined mutations in APP lie within β- or γ- secretase cleavage sites and they are showed in cell culture researches and transgenic mice to increase cleavage at these sites (18), that leads to an increased production of Aβ and Aβ 42 (amyloidogenic form of the peptide) (19, 20). Amyloid plaques include extracellular deposits of Aβ peptide.

Presenilin 1 & Presenilin 2

According to discovery of various pathogenic mutations in APP, it would be clear that APP mutations only explain small part of EOAD (21). Only 1 year after the discovery of the first APP mutation, another AD linkage region, at 14q24, is presented by four independent researches (22, 23). Three years later, researcher found the responsible gene (PSEN1) and determine the first mutation that causing AD (21). PSEN1 plays a vital role in mediating intra membrane and it encodes a highly conserved polytopic membrane protein (24). Mutations of PSEN1 result in advanced generation of Aβ42 from APP. The increased rate of Aβ42/Aβ40 presents that the mutations alter the position of the γ-secretase cleavage of APP (25).

The PSEN1 gene includes 10 protein-coding exons. It also consists of 2 to 3 additional exons encoding the 5'- untranslated sites. Alternative splicing of exon-8 in this gene has been stated (21). The major RNA transcripts of PSEN1 gene are 2.7 and 7.5 kb. These are expressed in various locals of the human brain, skeletal muscle, kidney, pancreas, placenta and heart. The PSEN1 is a serpentine protein that includes 467 amino acids with nine transmembrane domains. This protein is cited in the nuclear envelope, endoplasmic reticulum and Golgi apparatus in mammalian cells (26).

PSEN2 is discovered soon after PSEN1 based on the existing data. PSEN2 (protein: PS2) is similar to PSEN1 at the genomic and protein level (27).This gene has been discovered to be sited on chromosome 1q. Mutations in PSEN2 will be resulted in LOAD. In comparing with APP or PSEN1 mutations, the disease will be progressed slowly.

The PSEN-2 gene includes 10 protein-coding exons and two other exons encoding the5'-untranslated site. The PSEN-2 is also a serpentine protein that includes 448 amino acids with6-9 transmembrane domains. In structure, the PSEN-2 is similar to PSEN-1, but the mutations are located in different codons in compare with the PSEN-1.

It is stated that about 1/3 of dominantly inherited AD cases are not related with discovered mutations in either the APP or PSEN genes. It implies the existence of further disease loci (28).

Tau

In 1980s, various researches discovered that the main protein combining neurofibrillary tangles (NFTs) was the microtubule-associated protein (tau) (29-31). Tau is one of the microtubules associated proteins that are considered to have an important role in the stabilization of neuronal microtubules. NFTs are accumulation of filamentous tau polymers that consist of a portion of the fibrillar pathologies in AD. The frequent tau capacities are not limited to AD only, but they are also characteristic of frontotemporal dementias, progressive supranuclear palsy and corticobasal degenerations.

Finding out of mutations in the tau gene is connected to chromosome 17 (FTDP-17) in familial frontotemporal dementia. It has thrown light on AD mechanisms (32). Tau is a phosphoprotein. It found in neurons in the peripheral and central nervous system where it is linked with microtubule binding and assembly in axons that are necessary for axoplasmic transport (33).

A few of tau isoforms are resulted from a single gene by alternative mRNA splicing. Tau has six main isoforms in the human brain (around 352 and 441 amino acid residues). It differs by having 3 or 4 semi-conserved repeats of 31 residues in the MT-binding assembly domain and 0-2 insertions in the N-terminal projection domain (34, 35). They differ from each other by the presence or

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absence of three axons. The longest human brain tau isoform has 11 axons (36, 37).
Tau plays a clear role in AD, but the mechanisms of tau that produce dysfunction and death of neurons remain incompletely understood.

Late Onset Alzheimer Disease

There are several genes that investigated in relation with late onset Alzheimer disease. Twenty important genes associated with Alzheimer disease are shown in Table 2. The important involved genes are described in below.

Table 2: Twenty important genes associated with Alzheimer Disease (49)

	Gene symbol	Description	Category	Gene ID
1	APP	Amyloid beta (A4) precursor protein	Protein- coding	GC21M027252
2	COL25A1	Collagen, type XXV, alpha 1	Protein- coding	GC04M109731
3	BPTF	Bromodomain PHD finger transcription factor	Protein- coding	GC17P065821
4	PSEN1	Presenilin 1	Protein- coding	GC14P073603
5	PSEN2	Presenilin 2	Protein- coding	GC01P227058
6	CLSTN1	Calsyntenin 1	Protein- coding	GC01M009789
7	APOE	Apolipoprotein E	Protein- coding	GC19P045408
8	GSK3B	Glycogen synthase kinase 3 beta	Protein- coding	GC03M119540
9	CHAT	Choline O-acetyltransferase	Protein- coding	GC10P050817
10	APBB1	Amyloid beta (A4) precursor protein-binding, family B, member 1 (Fe65)	Protein- coding	GC11M006414
11	PSENEN	Presenilin enhancer gamma secretase subunit	Protein- coding	GC19P036236
12	LRP1	Low density lipoprotein receptor-related protein 1	Protein- coding	GC12P057497
13	NCSTN	Nicastrin	Protein- coding	GC01P160313
14	CDK5R1	Cyclin-dependent kinase 5, regulatory subunit 1 (p35)	Protein- coding	GC17P030813
15	GSK3A	Glycogen synthasekinase 3 alpha	Protein- coding	GC19M042734
16	CASP3	Caspase 3, apoptosis-related cysteine peptidase	Protein- coding	GC04M185548
17	APBA1	Amyloid beta (A4) precursor protein-binding, family A, member 1	Protein- coding	GC09M072042
18	APBA2	Amyloid beta (A4) precursor protein-binding, family A, member 2	Protein- coding	GC15P029213
19	CASP2	Caspase 2, apoptosis-related cysteine peptidase	Protein- coding	GC07P142985
20	MAPT	Microtubule-associated protein tau	Protein- coding	GC17P043971

Apolipoprotein E (APOE)

APOE denotes gene and apoE denotes protein. APOE is a protein with roles in lipid metabolism and tissue repair. APOE has been reported to mediate neuronal protection, repair and remodeling through a number of mechanisms that include antioxidant effects, interactions with estrogen and modulation of synaptodendritic proteins. Three different APOE alleles (e2, e3 and e4) found in human brain that lead to three common isoforms (e2, e3 and e4) with frequencies of 7 percent, 78 percent and 15 percent, respectively (38). In most old adults the e3 allele is the most frequent, while e4 occurs more often slightly than e2 (39). APOE e4 allele is a major risk factor for AD and also overshadows the genetic susceptibility to the effects of several forms of brain injury(40,41). A study by Teasdale et.al (42) showed that individuals with history of head injury had a poor initial response than non- APOE e4 individuals.
The largest study gathered data from 43 studies about APOE and AD. It involves information from 5930 AD patients and 8607 controls without dementia (11). Increasing e4 alleles in relation with dose - dependent increase was reported in this study. Findings have been supported by more recent meta-analysis that using largely overlapping data taken from the AlzGene database (43). De-

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spite, the frequency of e4 allele in the general population, a few AD patients investigated with the APOE e2 allele (44). It can be concluded that APOE e2 allele is protective against the development of dementia (11, 43-45).
The strength of the relationship varies among epidemiological studies. The APOE e4 allele is found to be neither necessary nor sufficient to cause AD.

Dynamin (DNM)

Another gene, DNM2 has been found in some studies to be related to LOAD in a Japanese population. However, the relation has been stated to be especially significant in subjects with non-APOE e4 carriers (46). In non-APOE e4 carriers two SNPs have been reported to be associated with LOAD. β-amyloid, which is stored in the AD brain interacts with dynamin 1 gene. DNM 2 gene is homologous to dynamin 1 and is located on chromosome 19p13.2 where a susceptibility region has been detected by linkage analysis. Expression of DNM 2 as well as DNM 1 is down regulated by β-amyloid in hippocampal neurons (47), suggestive of the involvement of dynamin proteins in the cascade of neurodegeneration caused by β-amyloid. Dynamin binding protein (DNMBP) gene cited on chromosome 10 has also been related to LOAD (48). Nevertheless, the mechanism by which the DNM2 gene causes the disease is not clear. Researchers have reported a decrease in the expression of hippocampal DNM2 mRNA, but it is not clear whether the decrease in the DNM2 expression is the cause or outcome of AD.

Associated chromosomes with AD

According to the data gathered from genome-wide linkage analysis and linkage disequilibrium studies, several studies have reported presence of candidate genes on multiple chromosomes, with highest Likelihood of Disease (LOD) score on chromosomes 12, 10, and 9. Among all the chromosomes, the linkage on chromosome 10, which has been presented in a number of non-overlapping samples, is the most prominent (49-52). Relation to chromosome 10q was expressed in a two - stage genome scan that involving 429 affected sibling pairs with probable or definite AD (53, 54).Significant signs about susceptibility region was identified on chromosome 10q21.2, with the most likely location of a risk gene at 78 cM. The study by Hamshere et al. did not show signs for a second locus on chromosome 10q25 - 26 as reported elsewhere (46, 50, 55).
Associations with chromosome 9 were described by Pericak - Vance and colleagues, firstly (56). They determined a high multipoint LOD score of 4.3 around 9p22.1 when limiting their analysis to sibling pairs with autopsy - confirmed AD. In addition, other researches determine that relation with this region is strongest in families with a minimum age of onset between 60–75 years (57). Practical support for this is complex. Some studies have showed evidences for a gene (or genes) in this region (52-54), while others have not (50, 51, 58).

Family and twin studies in AD

Twin studies aim to determine the genetic heritability of late - onset AD. Raiha et al. (59) performed a population - based study by using Finnish twins. Among 13,888 pairs, they found that the pair wise concordance among monozygotic (MZ) twins were 31 percent in compare with 9 percent among dizygotic (DZ) pairs.
Swedish study of dementia on twins reported findings from twins who were developed apart, and a control group of pairs who were grew up together (60). The concordance rate for MZ twins for AD was 67 percent in compare with 22percent among DZ twins, resulting in a heritability estimate of between75% and 85%.
Series of studies performed to indicate the proportion of AD risk attributable to genetic factors. The studies expressed that combination of environmental and genetic risk factors increase susceptibility to LOAD. Totally, the risk of AD for individuals with history of first degree relatives is around 32% and 49%, approximately two to four times more than control groups (61-64).
In Table 3 a summary of findings on potential risk factors for AD is showed (65).

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Table 3: Summary of potential risk factors for AD

Direction of association	Factors	Level of evidence
Increased risk	• APOE e4 genotype • Conjugated equine estrogen with methyl progesterone	Moderate
	• Some non-steroidal anti-inflammatory drugs* • Depressive disorder • Diabetes mellitus • Hyperlipidemia in mid-life • Traumatic brain injury in males • Pesticide exposure • Never married, less social support • Current tobacco use	Low
Decreased risk	• Mediterranean diet • Folic acid • HMG-CoA reductase inhibitors (statins) • Higher levels of education • Light to moderate alcohol intake • Cognitively engaging activities • Physical activity, particularly high levels	Low
No association	• Vitamin E • Cholinesterase inhibitors*	Moderate
	• Anti-hypertensive medication • Conjugated equine estrogen • Omega-3 fatty acids • Vitamins B12, C, beta-carotene • Homocysteine • Hypertension • Obesity • Metabolic syndrome • Early childhood factors • Occupational level • Lead	Low
Inadequate evidence to assess association	• Saturated fat intake • Fruit and vegetable intake • Trace metals • High caloric intake • Memantine • Sleep apnea • Anxiety disorders • Resiliency • Non-cognitive, non-physical leisure activities • Agent Orange, Gulf War Syndrome • Solvents, aluminum • Genetic factors other than APOE	Not applicable

Conclusion

Aging is the most obvious risk factor for developing AD. Moreover, several other possible biological (like; genetic alterations and polymorphisms, and abnormal immune or inflammatory responses) and environmental factors (like; education, traumatic injury, oxidative stress, drugs, and hormone

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replacement) and the interactions among these factors have been seemed to be contributors to a common pathway resulting in AD (66, 67).
According to the time of onset, genetic risk factors divided into two groups: Early-Onset and Late-Onset. The most of studies on foundation of AD are related to early-onset, because the genetic basis of early-onset AD is understandable but late-onset AD detected as a multi-factorial disease.

Family and twin studies indicated that there is a genetic basis for AD, of course this relation is not complete but it is significant. Therefore, studies looked a specific gene for AD. Genes involved in these processes, including APP, Presenilin1, Presenilin1/2, APOE, DNM, and Tau and so on, play important roles in AD initiation and progression. Moreover, the progression of AD is so important. Therefore, the Alzheimer's disease progression is showed in Fig. 1.

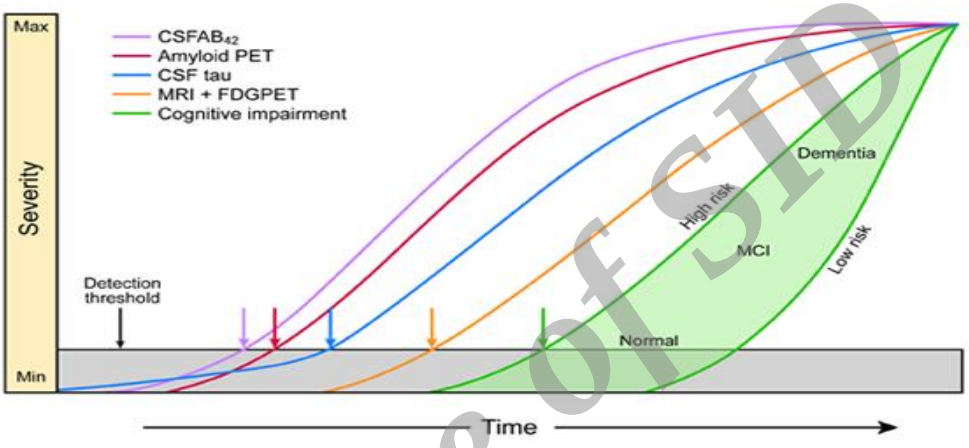

Fig. 1: The Alzheimer's disease progression (68)

This diagram shows how AD-related changes may occur in the brain before symptoms of cognitive decline first appear in people with mild cognitive impairment (MCI). The curves show the sequence in which specific markers may play a role as people progress from normal cognition, to MCI, and to dementia. This model explains that in typical LOAD, tau changes may begin before amyloid changes, but that amyloid changes occur faster and are the first ones detectable. It suggests that amyloid accumulation drives of progression tau and other downstream events in the disorder (68).
Despite the improvements in understanding different aspects of AD, the accurate risk factors of AD remain unclear. All of the findings that mentioned above are not generalized to all patients but included specific patients and none of theories alone is sufficient to explain the diversity of biochemical and pathological abnormalities of AD.

Ethical Consideration

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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