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Unusual Mechanism in Gene Mutation Associated With Alzheimer's Disease

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Abstract:

Alzheimer's disease has become a very common disease, which is a neurological disorder disease. This was expected that the rate of patients will be increased every year. One fact of factor that can develop Alzheimer's disease is family history. The identification of the ε4 allele of Apolipoprotein E can influence the risk of late-onset AD susceptibility for ~50%, Following genome-wide association studies and enormous parallel resequencing efforts, at least 21 new genetic risk loci for the genetically complicated form of AD have recently been discovered. This review aims to elucidate the causes of the heterogeneous genetic underpinnings of late-onset AD (LOAD). The resulting distinct dementia might be associated with different types of mutations. These results suggest that small structural or quantitative protein differences may be linked to a variety of clinical consequences

Keywords **—Alzheimer's disease, Genome-wide association studies, Late-onset AD**

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I. INTRODUCTION

Alzheimer's disease (AD) has become a very common disease, which is a neurological disorder disease. This was expected that the rate of patients will be increased in every year (1, 2). One fact of factor that can develop Alzheimer's disease is a family history (1, 3). Including AD has extremely heritable ($h2 = 58\%$-79%), but the genetic component was thought of as the similar variables discovered (4, 5). The mutation of AD has many patterns (6). One is rare mutations in *APP*, *PSEN1*, and *PSEN2* that are always caused by early-onset, which accounts for ~5% of it (7, 8). Another factor is caused by gene polymorphism, such as ε4 and ε2 of the APOE gene can affect ~50% susceptibility of common-onset AD (9, 10). And AD sometimes due to rare variants (11, 12). The genome researchers have identified AD associations with limited in relatively few genes, including TREM2, AKAP9, UNC5C, ZNF655, IGHG3, and CASP7 (13-18).

It is known that multiple factors were reported to involve in late-onset AD (LOAD) (19). Genetic preposition, however, thought to be a strong relationship with LOAD (20, 21). Multiple studies have explained that complex genetic components and heterogeneous factors were involved in the transmission and mutation of genes (or polymorphisms) that may interact with external factors like environmental factors (22, 23). APOE was the gene that has been reported to be the critical factor regarding the risk of developing AD (22, 24). This review aims to elucidate the causes of the heterogeneous genetic underpinnings of late-onset AD (LOAD).

II APOLIPOPROTEIN E

APOE is the gene that encodes a polymorphic glycoprotein found in many tissues such as the

brain and liver, and it can be found in immune cells, including monocytes and macrophages (25, 26). The primary role of ApoE is transporting lipid and cholesterol, especially in the brain, for many purposes, for example, neuronal growth and regeneration, repair process, brain tissue injury, immunoregulation, and activation of lipolytic enzymes (27, 28). There were three major allelic variants of APOE gene in a single locus which were ε2, ε3, and ε4 that encoded distinct isoforms of ApoE2, ApoE3 ApoE4 proteins (29). Each isoform of ApoE2, ApoE3 ApoE4 were two positions different of amino acids sequence (30, 31). In addition, APOE ε4 allele was reported to be the cause involved in an increased risk of developing most in early-onset and late-onset AD (32). However, clear evidence on this claim is still needed (33). The risk impact is evaluated as three times for heterozygous carriers (APOE ε34) and also 15-fold for ε4 homozygous carriers (APOE ε44) (34). To incorporates a dose-dependent manner onset age (35). The APOE ε2 allele is supposed a defensive impact (OR = 0.6) and to discontinuation in late-onset age (36, 37). As a common community possesses showed the 20–25% or more ε4 alleles, 40–65% of AD patients are ε4 carriers (38, 39). ApoE attaches to Aβ and effectuates the clearance of soluble Aβ and Aβ agglomerations, and ApoE ε4 is been less proficient in regulating the clearance of Aβ (40, 41). The impact of APOE ε4 accounting for 27.3% of the evaluated malady inheritance of 80%. The unaccounted-for percentage of heredity has fueled decades of ongoing research into genetic variables linked to disease (42, 43). Decades of continuing study into the genetic risk factors for numerous diseases has been driven by the component of heredity that had not yet been accounted for (44).

III GENOME-WIDE ASSOCIATION STUDIES

Gene-expression network analysis has discovered quality systems and frequent and rare genetic variants connected to LOAD, as well as genome-wide association studies (GWAS) and whole-genome sequencing (WGS) (45). These genes are found in pathways, such as cholesterol digestion, endocytosis, and the immune system (innate immunity) (46). The GWAS determined both gene and microglial cells as critical factors within the prognosis of AD (47, 48). The GWAS have stimulated an abundance of genotype and phenotype association research, the majority of which employ GWAS proxy single-nucleotide polymorphisms (49). The majority of progress has been achieved in the genes identified enough in GWAS, with efforts to identify the variations responsible for each locus remaining restricted (50).

However, the precise role of microglia is unknown but it may directly contribute to AD pathology, according to genetic and early functional studies (51). This study summarizes numerous genes linked to increased risk and those related to the immune system that was discovered in these investigations. By examining the role of microglia in AD, was identify be able to uncover new treatment targets for Alzheimer's disease by studying the involvement of microglia in the illness. Collaborative research GWAS and the Global Genetics of AD had considerably expanded our understanding of the genetic basis of late-onset AD by discovering at least 20 new genetic risk loci (52). Notably, The risk alleles that underpin these GWAS findings are mostly unknown. This has ramifications for how these discoveries are translated into molecular mechanisms and the generation of precise epidemiological estimates such as the population-attributable fraction and risk prediction at the individual level (53).

According to GWAS studies, Clusterin (*CLU*) showed that this gene was the first new risk gene for AD. This gene may be contributing to AD Neurodegeneration by regulating aggregation and endocytosis removal from the brain, as well as lipid transport and inflammation. Targeted resequencing of *CLU* demonstrated an increased frequency of uncommon code *CLU* variants, irrespective of the general association signal reported, It has been established that variety variations (rare coding and common regulative variant) exist and recent research has demonstrated rare variants linked with enhanced penetration in the case of Sortilin-related receptor 1 (*SORL1*) and ATP-binding A member 7 (*ABCA7*) cassette (54, 55).

SORL1 was found to be a risk factor for late-onset AD, which was later confirmed in the recent GWAS meta-analysis (56). While the approximate linear variations for these link signs are unknown, studies on human induced pluripotent stem cells suggest that these genetic variations may impact enhancers of BDNF-mediated *SORL1* expression and APP processing. To some extent, whole-exome sequencing revealed a few mutations in *SORL1* was with autosomal dominant early-onset AD. In contrast, more variations of *SORL1* have been found for selective resequencing for late-onset AD patients that impact APP processing and AD etiology (57). The *ABCA7* gene has been found to be a risk factor for AD in large-scale studies, with high expression levels observed in hippocampal neurons, an early brain region to be affected by AD, and in microglia (58). Although some believe that *ABCA7* may interact with APOE and lipid metabolism and clear Aβ aggregates from the brain, it remains unclear whether it does so through functioning as an immune system molecule and interacting with APOE (59). *ABCA7* is related to AD risk variants in the brain, but the findings have been inconclusive. In more recent times, a higher incidence of rare pathogenic mutations in *ABCA7* has been mentioned in AD patients, with a tendency for the disease to manifest as an autosomal dominant inheritance pattern (60).

The recycling of synaptic vesicles, a process essential for each synaptic release, is involved in clathrin-mediated endocytosis, which is the job of bridging integrator 1 (*BIN1*). The highly factors that expression in the human brain was *BIN1* this also correlated with an increased risk of disease onset and a shorter duration of the disease in AD patients, leading to a 4.5-fold increase in transcriptional activity in vitro, with consequent higher levels of *BIN1* expression in the human brain and increased risk of Alzheimer's disease. Additionally, studies have revealed an increased level of P-tau181P in cerebrospinal fluid of AD patients, and the Drosophila ortholog Amph modifies tau neurotoxicity, furthering the hypothesis that BIN1 may mediate risk by contributing to Tau pathology.

IV GENES IDENTIFIED THROUGH COMMON VARIANTS IN GWAS

A. CR1

Complementary protein 1 (CR1) is an immune-based cell-expressed glycoprotein, including microglia. Chromosome 1q32 of its encoding gene, *CR1*, contains four different alleles that differ in populations in sizes, transcription, and frequency (61, 62). The *CR1* is the principal receptor of complement C3b via the complementary cascade in controlling immunological response. The cascade supplement is known for mediating microglial activity with the cutting of synapses. The C1q complement system, which binds with the CR1, was activated by Aβ (63, 64). Increased CR1 is linked to exacerbated microglia but it blocking CR1 prevents Aβ microglia. However, because CR1 is produced in a range of cell types in brain cells and immune cells, Whether CR 1 causes AD in one cell or via all the cells it expresses was not determined by its effect (65).

B. CELF1/SPI1

The SNP rs10838725 is found in the gene *CELF1*, and IGAP's meta-analysis identified it as a risk factor for AD. However, because learning disorders are common in this population, there may be other genes linked to AD. In LOAD, the *SPI1* was a problem (66). The researchers found five changes in myeloid cells that interact with AD and *SPI1*. The PU.1 cistrome, which covers the neurotransmitter throughout the genome, was enriched in AD. According to chromatin immunoprecipitation (ChIP)-Seq results from myeloid cells showes that PU.1 binds *TYROBP*, *MS4As*, *INPP5D*, *TREM2*, and *CD33 (67)*. This is a metric for gene expression regulation (68).

C. MS4A family

MS4A4A, *MS4A4E*, *MS4A6A*, and *MS4A6E* have all been linked to AD these were located on chromosome 11q12 and include eighteen genes spanning approximately 600kb (69). In peripheral primary human monocytes in brain tissue and neural cells, the SNP was linked to chromatin markers that indicated reduced transcription and

improved and active transcription sites. Another SNP, rs670139, is found between *MS4A4A* and *MS4A6A* and is linked to an elevated risk of LOAD (70). *MS4As* are more expressed in peripheral immune cells and are found in microglia and macrophages in the brain. These *MS4A4A* and *MS4A6A* proteins include ligands for the signaling pathway PU.1, which would also be produced only in myeloid cells and associated with AD (69, 71).

D. ABCA7

A type of transporter that transports ATP is the ATP-binding channel carrier (ABCA7) (72). *ABCA7* is located on the 19p13.3 chromosome this is a protein that transports phospholipids to apolipoproteins, such as APOE and APOJ/CLU, and the mutations in *ABCA7* may affect AD via. *ABCA7* also has been related to microglial phagocytosis and clearance, implying that it could be a microglial activity regulator (59, 71). The number of unusual coding mutations in *ABCA7* causes it to lose function, increasing the risk of AD (55, 56).

E. TREM2

TREM2 is a membrane protein that recognizes lipids produced after cell damage and serves as a receptor complex of myeloid immune cells (15, 16). TREM2 is linked to the TYROBP/DAP12 protein kinase, which is critical for subsequent signal transmission through this transmitter (73). *TREM2* has been related to a number of genes, some of which have previously been connected to the risk of AD, which could be a compensatory strategy because *TREM2* mutations in AD cause a complete functionality ability loss and potentially impair *TREM2* receptor securing to its related ligands (17). The very same genetic variants were related to an elevated risk of several neurological disorders, including Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal lobar degeneration (FTLD). *TREM2* is expressed selectively in microglia, and its connection with other immune genes, as well as to reduce the function of *TREM2* mutation in microglia, indicating it is very important in LOAD (74, 75).

CONCLUSIONS

Alzheimer disease, which affects memory and cognitive abilities, is defined by an irreversible, progressive loss of memory and cognitive abilities that can occur in rare familial situations. Alzheimer's disease has no cure at the moment, and treatments are only helpful in delaying the progression of the illness in certain people. Different mutations in the same gene or a mutation's dosage variable may be linked to the ensuing unique dementia. These findings imply that minor structural or quantitative changes in proteins might be connected to a range of clinical outcomes. These genotypes can help researchers learn more about the pathogenicity of these mutations and help them discover novel treatment targets. The Genome Correlation Study (GWAS) studies the relationships between different bases in the genome of a cohort of people in the genome. but these are some of the limitations presented by GWAS that dictate that all target placements work sequentially to determine which genes have impacted these mutations. Prioritizing SNPs and determining which can have the most effects on gene function utilizing computational algorithms that incorporate information such as transcription state, chromatin state, DNA methylation, splicing, and gene expression.

The GWAS that identified the loci has not contained the genes in whole-brain tissues, The result of cell-type heterogeneity. Microglia have a feature that is similar to gene expression and relations with other myeloid lineage end immunological cells. The various views showed microglia have a role in the etiology of AD and the monocytes and macrophages cells can implicate by themselves or can combine with other microglia to observe the immunological effect.

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