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Unraveling the genes implicated in Alzheimer's disease (Review)

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Abstract. Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder and it is the most common form of dementia in the elderly. Early onset AD is caused by mutations in three genes: *Amyloid-β precursor protein, presenilin 1* (*PSEN1*) and *PSEN2*. Late onset AD (LOAD) is complex and apolipoprotein E is the only unanimously accepted genetic risk factor for its development. Various genes implicated in AD have been identified using advanced genetic technologies, however, there are many additional genes that remain unidentified. The present review highlights the genetics of early and LOAD and summarizes the genes involved in different signaling pathways. This may provide insight into neurodegenerative disease research and will facilitate the development of effective strategies to combat AD.

Contents

1. Introduction

Alzheimer's disease (AD), the most common form of dementia among older adults. It is a progressive neurodegenerative disorder, which has been widely recognized as worldwide challenge for society and health-care providers. Clinically, it is defined by progressive loss of cognitive functions, ultimately leading to dementia and mortality (1). Neuropathologically, AD is characterized by the aggregation and deposition of misfolded proteins, in particular aggregated amyloid-β (Aβ) peptide in the form of extracellular senile (or neuritic) plaques and hyperphosphorylated tau protein in the form of intracellular neurofibrillary tangles (NFTs) (1). Early onset AD (EOAD) affects <1% of all AD cases with autosomal dominant inheritance. Late onset AD (LOAD) characterized by a genetically complex and high hereditary pattern of inheritance, is the most common form of the disease with an age of onset >65 years (2). Evidence indicates that the major factor of AD pathogenesis is due to abnormal aggregation and clearance of Aβ by apolipoprotein (Apo) E. However, other potential mechanisms, including modulation of neurotoxicity and tau phosphorylation by Apo E, synaptic plasticity and neuro-inflammation have not been eliminated (3).

The latest advancement in genome wide association studies (GWASs) revealed various candidate genes, which illustrates that LOAD is governed by an array of low penetrance common risk alleles across a number of different loci. EOAD is inherited through an autosomal dominant pattern and is predominantly governed by three rare mutation genes: APP, PSEN1, PSEN2, however, the genetics of LOAD is much more complex. As a result, a large proportion of the heritability of AD remains unexplained by known disease genes (1). In the present study we will have a simple overview of the most susceptible genes of LOAD (sporadic AD), EOAD, and relationship between these genes and the pathogenesis of AD.

2. Associated and susceptibility genes of EOAD

EOAD is inherited in an autosomal dominant fashion, which is governed by a rare mutation in three genes: *Amyloid precursor protein* (*APP*) on chromosome 21q, *presenilin 1* (*PSEN1*) on 14q and *presenilin 2* (*PSEN2*; a homolog of PSEN1) on 1q. Mutation in these three genes causes AD with high penetrance in mutation carriers (1), with Aβ peptide volume overload and collectively accounts for <1% of AD cases in the population. Studies have indicated that rare mutations in these genes exert little effect on or even have no association with LOAD, which indicates that these three gene loci alone do not explain the underlying mechanism of LOAD (Table I).

APP. Located on chromosome 21, APP was the first gene discovered to be associated with EOAD. APP is an integral membrane glycoprotein expressed in the brain and central nervous system (CNS) (4). There are two signaling pathways associated with proteolytic cleaving: The α and β pathway, and the former is the most common. The main neuropathological hallmarks of AD are senile plaques and NFTs, which may be associated with brain atrophy and cerebral amyloid angiopathy.

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Table I. Hereditary AD.

Name	Associated gene	Locus	Functional pathway
AD1	*APP*	21q21.3	Aβ generation
AD2	Apolipoprotein E	19q13.32	Mediate Aβ levels\lipid transport cholesterol
AD3	Presenilin 1	14q24.2	Aβ clearance and production
AD4	Presenilin 2	1q42.13	Mediate Aβ level
AD5	LDL receptor related protein 1	12p11.23-q13.13	Mediate endocytosis\signaling pathways
AD6	Calcium homeostasis modulator 1	10q24	Calcium metabolism
AD7	-	10p13	-
AD8	Cystatin C	20p	Mediate Aβ level\Interact with *APP*
AD9	-	19p13.2	-
AD10	-	7q36	-
AD11	-	9p22.1	-
AD12	-	8p12-q22	-
AD13	-	1q21	-
AD14	-	1q25	-
AD15	Nicotinamide nucleotide adenylyltransferase 3	3q22-q24	Nicotinamide adenine dinucleotidemetabo lism\Ca^{2+} signaling pathways
AD16	Protocadherin 11 X-linked	Xq21.3	Calcium metabolism
AD17	Triggering receptor expressed on myeloid cells 2	6p21.1	Mediate Aβ level\inflammation

AD, Alzheimer's disease; APP, amyloid-β precursor protein; Aβ, amyloid-β.

The primary component of senile plaques is Aβ peptides, which are partially generated by the APP gene; although APP acts as the precursor protein for Aβ. Endoproteolytic cleavage of APP by two secretases enzymes, β-secretase and γ-secretase, produces Aβ. In the majority of cases, the γ-cleavage produces Aβ40, although it also generates a more toxic variant, Aβ42 (5). Notably, the catalytic center of γ-secretase is encoded by the EOAD genes, *PSEN1* and *PSEN2* (1). Mutation in the *APP* gene leads to an increased quantity of Aβ, which is 2-to 3-fold higher than normal or non-mutated APP (6). Under normal circumstances, α-secretase cleaves APP to produce secreted APP (sAPP) α and membrane-bound C83, while in the amyloidogenic signaling pathway APP is first cleaved by β-secretase to produce sAPPβ, and subsequently by γ-secretase to yield Aβ and carboxy-terminal fragment (CTF) γ (7). The amyloid cascade hypothesis is the most accepted explanation for the pathogenesis of AD, which suggests that Aβ is the principal component of AD pathogenesis (1).

PSEN1 and PSEN2. PSEN1 and PSEN2 have a similar structure and are associated with γ-secretase activity. Mutations in *PSEN1* (AD3) and *PSEN2* (AD4) were reported to increase the production of Aβ, which results in a larger production of Aβ42 than Aβ40, and Aβ42 tends to be more amyloidogenic and aggregates more easily than Aβ40 (8). PSEN1 mutations may also be associated with cotton wool plaques (9). PSEN2 has a very similar structure and function to PSEN1. Mutations in PSEN2 affect γ-secretase activity and thus result in an abnormal production of Aβ42.

ATP binding cassette subfamily A member 2 (ABCA2). Recently, an *in vitro* study demonstrated that ABCA2 was highly expressed in the human neuroblastoma cell line and overexpression of ABCA2 increased transcription of the APP protein (10). A previous study (10) evaluated the temporal and frontal cortex in normal and AD brains, and showed that ABCA2-transfected cells were more resistant to a free radical initiator, which indicated the involvement of ABCA2 in protection against reactive oxygen species and suggested an association with AD. Macé *et al* (11) found a significant association between a C-T single-nucleotide polymorphism (SNP) in exon 14 of the *ABCA2* gene (rs908832) and AD in a large case-control study involving 440 AD patients, suggesting a strong association between *ABCA2* and EOAD (11).

Catenin α3 (CTNNA3). CTNNA3 is a binding partner of catenin β 1 (CTNNB1). In turn, CTNNB1 interacts with PSEN1, which has many mutations that elevate Aβ42 expression levels and cause early onset familial AD. CTNNA3 was reported to have significant association with LOAD (12) and was also associated with LOAD in females (13).

Prion protein (PRNP). The *PRNP* gene encodes the prion protein (PrP), which has been implicated in various types of transmissible neurodegenerative spongiform encephalopathies. Being a major component of amyloid plaque, it may increase the risk of AD due to the pathogenic formation of amyloid-like fibrils. There are two wild-type variations in the frequency of V129 and M129 alleles of the *PRNP* gene. Compared with those with the MV or MM genotypes, those with the 129VV genotype demonstrate a greater decline in cognitive performance (14). Dermaut *et al* (14) identified significant association between homozygosity for 129VV and EOAD among 123 Dutch patients, which was stronger in those individuals with a family

Table II. Sporadic genes associated with Alzheimer's disease.

Gene	Locus	Functional pathway
ABCA2	9q34.3	Mediates Aβ level
ACE	17q23.3	Metabolism
APBB2	4p14-p13	Mediates Aβ level
A2M	12p13.31	Mediates Aβ level
BACE1	11q23.3	Mediates Aβ level
BIN1	2q14.3	Mediates Aβ level
BLMH	17q11.2	Against homocysteine toxicity
BSG	19p13.3	Neuroinflammation\immunoglobulin
CALHM1	10q24.33	Calcium metabolism
CAPS1	11q23	Mediates Aβ level
CD33	19q13.41	Inflammation\neuroinflammation
CLU	8p21.2	Neuroinflammation\lipid transport cholesterol
COL25A1	4q25	Senile plaques formation
CR1	1q32.2	Inflammation\neuroinflammation
CST3	20p11.21	Mediates cerebral amyloidosis
CTNNA3	10q21.3	Interact with PSEN1/mediate Aβ level
CYP2D6	22q13.2	Metabolism
GAL	11q13.3	Drug metabolism
HFE	6p22.2	Iron metabolism
HTR7	10q23.31	G-protein receptor\metabolism
IDE	10q23.33	Mediates Aβ level
LRP1	12q13.3	Signal transduction\metabolism
MAPT	17q21.31	Mediates tau level
MS4A	11q12.2	Inflammation\neuroinflammation
MPO	17q22	Antimicrobial oxidant\inflammation
NOS3	7q36.1	Metabolism
PICALM	11q14.2	Mediates Aβ level
PLAU	10q22.2	Mediates Aβ level
PRNP	20p13	Formation of amyloid-like fibrils
SORL1	11q24.1	Mediates Aβ level
UBQLN1	9q21.32	Mediates Aβ level

history. In a previous study of 482 AD patients, including 138 with onset aged <60 years, Riemenschneider *et al* (15) found that the 129MM genotype conferred an increased risk of developing AD in the early onset group (odds ratio, 1.92; P=0.013), which was more marked in those patients without the *APOE* ε4 allele. This demonstrated that individuals exhibiting heterozygosity for a common polymorphism in the human PrP confer more resistance to prion diseases (15).

3. Genes that confer susceptibility to LOAD/sporadic AD

The underlying mechanism of mutations in genes causing LOAD is markedly more complicated than that of EOAD. To date, Apo E is the only unanimously accepted genetic risk factor for the development of sporadic AD and the ε4allele for *APOE* has been implicated in LOAD (1). However, there are numerous susceptibility genes associated with LOAD (Table II), with the predominant function of certain susceptibility genes being mediating Aβ expression levels, whilst others are implicated in metabolic pathways.

Genes that mediate Aβ expression levels

APOE. Located on the long arm of chromosome 19, the *APOE* gene is confirmed as a susceptibility gene locus of AD, which is significant in familial and sporadic AD cases. *APOE* is considered to be a genetic risk factor rather than a disease-causing mutation for LOAD. The three most common SNPs in the *APOE* gene lead to changes in the coding sequence and result in three common forms of Apo E: Apo E ε2 (cys112, cys158), Apo E ε3 (cys112, arg158)and Apo E ε4 (arg112, arg158). Apo E is key in lipoprotein metabolism and cholesterol transport in plasma and the nervous system (1). Sufficient evidence indicates that different forms of Apo E have diverse effects on the aggregation and clearance of Aβ (16). Apo E ε3 is the most common form of all the *APOE* alleles, which serves a more significant role than Apo E ε4 in delivering cholesterol to neurons. Apo E ε2 is associated with a decreased risk for AD, while Apo E ε4 is regarded as the strongest risk factor for AD. Compared with Apo E ε4, Apo Eε2 and Apo E ε3 may enhance the clearance of Aβ and thus Apo E ε4 may be associated with an increased risk for LOAD (3).

Previous studies have found that Apo E ε4 was more efficient than Apo E ε3 and Apo Eε2 in increasing Aβ40 aggregation (3,17,18). Apo E may be important in the clearance of Aβ. Various *in vitro* studies have demonstrated that Apo E enhances cellular Aβ uptake and degradation; thus, the blood-brain barrier must be considered as a potential pathway of Aβ clearance in the brain, particularly via low density lipoprotein receptor-related protein1 (LRP1) (3,19). Apo E has been shown to promote the deposition of Aβ plaques and NFTs, thus leading to the development of AD (1).

Amyloid-β precursor protein binding family B member 2 (APBB2). The *APBB2* (or Fe65-like sequence; FE65L1) gene encodes for theAPBB2 protein. Li *et al* (20) performed a genetic association study of APBB2 and LOAD, and demonstrated that one SNP (rs13133980), located in a region conserved between the human and mouse genomes, was associated with age of disease onset. Golanska *et al* (21) found that severe cognitive impairment in centenarians was due to the over expression of APBB2 rs13133980 G.

Plasminogen activator, urokinase (PLAU). Urokinase plasminogen activator (uPA; *PLAU*) converts plasminogen to plasmin, which is involved in the processing of APP and degrades secreted and aggregated Aβ (22). The *PLAU* gene is located on chromosome 10, maps to the AD6 critical region, which is associated with LOAD, with allele C being a recessive risk allele and allele T conferring protection (22). A previous study by Ozturk *et al* (23) revealed that SNP rs2227571 in intron 9 and s4065 in the 3'- untranslated region (UTR) revealed a significant association with AD. Recently, a meta-analysis comprising 6,100 AD cases and 5,718 control subjects showed that the T allele of the rs2227564 polymorphism in the *PLAU* gene was associated with an increased risk of AD (24).

Triggering receptor expressed on myeloid cells 2 (TREM2). TREM2 is a transmembrane glycoprotein that consist of an extracellular immunoglobulin-like domain, a transmembrane domain and a cytoplasmic tail, which encodes a single-pass type I membrane protein that forms a receptor-signaling complex with the TYRO protein tyrosine kinase-binding protein (TYROBP, also termed DAP12) and, thereby, triggers the activation of immune responses in macrophages and dendritic cells (25-27). Previous studies have revealed the association of TREM2 with LOAD, and have also shown that a rare variant in this gene (SNP rs75932628-T) increases the risk for AD by up to 5-fold (26,28,29). Acting as an innate immune receptor and DAP12-associated receptor, TREM2 is expressed widely on the surface of cells, such as macrophages, microglia, osteoclasts and immature dendritic cells (30).

The expression level of TREM2 is high in white matter, moderate in the hippocampus and neocortex, but lowest in the cerebellum (28). A rare functional variant (R47H) in TREM2 has been associated with the pathological features reported in the AD brain and Nasu-Hakola disease, a rare form of autosomal recessive disorder, characterized by multiple bone cysts that leads to dementia associated with bone cystic lesions (27). In addition, loss-of-function mutations in TREM2 and DAP12 was associated with the Nasu-Hakola disease (25). Furthermore, homozygous and heterozygous loss-of-function mutations in TREM2 have been associated with early onset dementia, as well as with Nasu-Hakola disease (28). TREM2 is mainly associated with the clearance of neural debris, such as apoptotic neural tissue in the impaired nervous system. However, the endogenous ligand of the lesioned neural tissue that is recognized by TREM2 remains unknown (26). Furthermore, there is an anti-inflammation cytokine milieu subsequent toTREM2 combining with DAP12, which mediates the clearance of neural debris. The TREM2 variants (the R47H substitution) may exacerbate inflammatory cascades, thus inciting systemic inflammatory response and the death of neurons (27). There is a positive correlation between the increased TREM2 expression and increased cortical levels of Aβ; however, the dysregulation of expression that is induced by Aβ is relatively specific to TREM2 (27). Previous studies have also revealed the role of TREM2 in Aβ accumulation and ageing (31). Thus, TREM2 variants cause AD via downregulation of the Aβ phagocytic ability of microglia and via the dysregulation of the pro-inflammatory response of these cells.

Phosphatidylinositol binding clathrin assembly protein (PICALM). The association between AD and the gene encoding PICALM variants have been demonstrated in previous studies (32,33). *PICALM* is located on chromosome 11q14.2 and is largely restricted to endothelial cells, with a low expression level in neurons and glial cells. PICALM promotes clathrin-mediated endocytosis and facilitates with presynaptic endocytosis (34). PICALM has been associated with Aβ production and APP processing (33,34). Recently, the role of PICALM in tau clearance and autophagy wasimplicated as a multifunctional protein (35). PICALM interacts with bridging integrator 1 (BIN1) for the intracellular trafficking of proteins, lipids, growth factors and neurotransmitters. In addition, the intracellular trafficking of synaptic vesicle, vesicle-associated membrane protein 2, is conducted by PICALM, which is vital to memory formation and neuronal function. Furthermore, the PICALM protein is predominately expressed in endothelial cells, where it may contribute to Aβ clearance into the bloodstream (36). The transport of Aβ across vessel walls and into the bloodstream is a major pathway of Aβ removal from the brain, and the impairment of which is proposed to be important in the development of AD (36). An increased expression level of SNP rs3851179 located upstream of the coding region was found to be protective against AD (37). In addition, Schjeide *et al* (38) demonstrated that only rs541458 in PICALM was shown to affect cerebrospinal fluid (CSF) protein levels, suggesting that the AD risk allele is associated with decreased CSF Aβ42 expression levels, which provides an insight into the potentially predominant pathogenetic mechanism underlying the association between AD risk and PICALM (38).

BIN1. Located on chromosome2q14.3, *BIN1* has various forms and it is abundantly expressed in the brain. *BIN1* (also termed amphiphysin II) encodes various forms of an adaptor protein involved in receptor-mediated endocytosis, which may have an effect on Aβ production and/or the clearance of Aβ from the brain (1). BIN1 may bind to integrin α3 to mediate adhesion and detachment of migrating neurons from radial glial fibers in mice (39,40). Notably, BIN1 has been implicated in cell-to-cell communication and signal transduction (40,41). In addition to the locus, rs744373, near BIN1, a GWAS identified additional loci emerging simultaneously with *BIN1* from the SNPrs597668 near exocyst complex component 3-like 2/biogenesis of lysosomal organelles complex 1 subunit 3/microtubule affinity regulating kinase 4, which was associated with LOAD (41).

Sortilin-related receptor (SORL1). SORL1 encodes a mosaic protein that is a member of the vacuolar protein sorting-10 domain-containing receptor family and the low-density lipoprotein receptor family (42). SORL1 mediates the transport of vesicles from the cell surface to the Golgi apparatus and endoplasmic reticulum, which is vital in APP processing. According to Sager *et al* (43), decreased SORL1 expression levels reflects cognitive performance and may predispose individuals with mild cognitive impairment to the development of AD (43). Recently Louwersheimer *et al* (44) demonstrated that *SORL1* SNP rs2070045G allele was correlated with hippocampal atrophy and CSF-tau, suggesting the role of *SORL1* in AD pathology.

Insulin-degrading enzyme (IDE). IDE (also termedinsulysin) is a 110-kD neutral metallopeptidase that decreases the level of numerous of peptides, such as insulin and Aβ.IDE is involved in the clearance of extracellular Aβ (45). Extracellular IDE may be key in the clearance of Aβ and can be associated with AD. Furthermore, Apo E, which is major risk factor for LOAD, enhances IDE activity (46). In a previous study, a reduction of the IDE level by 50% in AD patients with the Apo E ε4 allele compared with those without the Apo E ε4 allele indicated that decreased IDE may be risk factor for AD (47).

α2-macroglobulin (A2M). The A2M gene is located on chromosome 12p13.31. The *A2M* gene encodes A2M, and it inhibits numerous proteases, such as trypsin, thrombin and collagenase (48). A2M acts as an extracellular chaperone and is involved in the clearance of extracellular Aβ (49,50). The role of A2M in inflammation and amyloid fibril formation suggests that A2M expression is critical in the pathogenesis of AD (51,52).

Ubiquilin 1 (UBQLN1). The gene coding for UBQLN1 is located on chromosome 9q22.2.*UBQLN1*, also termed proteins linking integrin-associated protein, has two haplotypes, haplotype H4, which is associated with AD risk andH5, which is associated with protection (53). UBQLN1 regulates APP maturation and acts as a chaperone for APP (54,55). Overexpression of UBQLN1 results in a reduced Aβ42/Aβ40 ratio while APP-induced toxicity is increased by knockdown of UBQLN1 (54). Thus, reduced UBQLN1 expression may contribute to the pathogenesis of AD.

Genes implicated in the metabolic pathway

Nitric oxide synthase 3 (NOS3). NOS3 gene encodes NOS3 and is located on chromosome 7q35. Nitric oxide (NO) may be involved in oxidative stress-induced neurodegeneration in AD (56). A meta-analysis by Liu *et al* (57) demonstrated that there was a significant association between the *NOS3* G894T polymorphism and risk of AD (57). Increased expression levels of Aβ and APP, and impaired spatial memory were demonstrated by Austin *et al* (58) in NOS-deficient mice. Thus, the pathogenesis of sporadic AD may results from a deficiency of endothelial NO.

Nicotinamide nucleotide adenylyltransferase 3 (NMNAT3) and calsyntein 2 (CLSTN2). NMNAT3 is located on chromosome 3q23. The SNP rs952797, which is downstream of the gene encoding NMNAT3 and upstream of the gene encoding CLSTN2, was demonstrated to be associated with AD (59). The *NMNAT3* gene is key in nucleotide adenylyltransferase (NAD) synthesis and involved in AD (60). Recently NMNAT3 deficiency was identified to be associated with hemolytic anemia (61).

Calcium homeostasis modulator 1 (CALHM1). CALHM1 is a key modulator of intracellular Ca^{2+} homeostasis, which maps to the AD6 region on chromosome 10q24.33 (62). Altered Ca^{2+} metabolism may lead to the development of AD (63). SNP rs2986017 polymorphism in the *CALHM1* gene has been associated with LOAD risk (62,64). In cohorts with an increased risk of AD, Koppel *et al* (65) revealed that the P86L polymorphism was associated with elevated CSF Aβ42 and Aβ40 levels. The latest findings demonstrated that a rare genetic variant in CALHM1 alters Ca^{2+} homeostasis and may contribute to the development of EOAD (66).

5-Hydroxytryptamine receptor 7 (5-HTR7). HTR7 is a G protein-coupled receptor for serotonin. According to Liu *et al* (59) HTR7 was associated with LOAD on chromosome 10q22-24. In their association study three SNPs, rs17129662, rs11185978 and rs7071717 together at 91.7 Mb, demonstrated an association with multiple cognitive domains in 197 unrelated subjects (59). Perez-García and Meneses (67) revealed that selective 5-HTR7 agonists are useful in the treatment of dysfunctional memory in aged-associated decline and AD.

Angiotensin-converting enzyme (ACE). The *ACE* gene is located on chromosome 17q23 and is expressed in the brain. ACE may influence Aβ metabolism (68). *In vitro* and *in vivo* studies have indicated that ACE functions to degrade Aβ and low ACE activity may increase the risk of AD (68,69). Although the association of ACE inhibitor and risk of AD remains unclear, Qiu *et al* (70) revealed a positive correlation between ACE inhibitor use and AD among APO ε4 carriers.

LRP1. LRP1 is located on chromosome 12q13.3 and is involved in intracellular signaling, lipid homeostasis and clearance of apoptotic cells. LRP1 mediates the transport of Aβ, which in turn prevents synaptic dysfunction and neurodegeneration (71).Impaired clearance of Aβ by LRP1 is associated with accelerated Aβand AD progression (71). Jaeger *et al* (72) also revealed that dysfunction of LRP1 at the blood brain barrier may be associated with increased Aβ accumulation and progression of AD. Recently, LRP1 was associated with downregulation of β-site APP-cleaving enzyme 1 (BACE1) and, thus, affects generation of Aβ by cleavage of the APP (73).

Genes regulating neuroinflammation

Membrane-spanning 4-domains (MS4A). The *MS4A* genes are located on chromosome 11q12 in humans. Proteins in the MS4A family share similar structures, amino acid sequence homology and chromosomal location. Various members of MS4A (including MS4A3, MS4A2, MS4A6A, MS4A4A, MS4A4E and MS4A6E) are significant in immunity, indicating the possible involvement of the *MS4A* gene cluster in AD pathogenesis (74). LOAD GWAS have identified various SNPs as follows; rs983392 and rs610932 at MS4A6A, associated with decreased AD risk, and SNP rs610932 near MS46A, associated with increased AD risk (75-77). The MS4A family modulates Ca^{2+} homeostasis and increased levels of intracellular Ca^{2+} lead to neuronal death. Thus, overexpression of the *MS4A* gene may result in immune system dysfunction.

CD33. CD33 is a transmembrane protein located on chromosome 19q13.3 that is expressed on myeloid cells and microglia (78). CD33 mediates endocytosis independent of clathrin and may be key in Aβ clearance. In LOAD GWAS, the CD33 rs3865444 polymorphism was associated with the risk for AD (75,76). Recently, Bao *et al* (79) revealed that the rs3865444 allele was associated with decreased AD risk; however, the association differed significantly between the Asian and Caucasian group. Bradshaw *et al* (80) identified that CD33 is important in Aβ clearance. The authors found that the ability of monocytes to phagocytose Aβ is inhibited by increased expression levels of CD33 on the surface of circulating monocytes (80).

Clusterin (CLU) and complement receptor 1 (CR1). Inflammation plays a primary role in the development AD. CLU and CR1 demonstrate marked responses to inflammation and innate or adaptive immunity. CR1 is the main receptor of the complement C3b protein, a key inflammatory protein activated in AD (81). CLU is one of the major Apo in the brain, and may be involved in synaptic turnover and apoptosis (82). Located on chromosome 8p21.1, SNP rs9331896 of CLU was associated with LOAD (77). The progression of AD and brain atrophy is significantly associated with increased plasma CLU levels (83). The *CR1* gene is located on chromosome 1q32, and is widely expressed on B lymphocytes, monocytes, macrophages, erythrocytes and dendritic cells (84). CR1 may be involved in innate and adaptive immune responses (85). In addition, CR1 is important in AD pathogenesis as it contributes to mediating neuroinflammation and activating the complement system (86). In LOAD GWAS, SNPs rs6656401 and rs3818361 were associated with the risk of LOAD (33). The plaque load in the brain of patients with AD was identified to be associated with SNP rs1408077 of *CR1* (87).

X-linked inheritance

Protocadherin 11 X (PCDH11X). PCDH11X/Y belongs to the protocadherin gene subfamily of the cadherin super family of cell surface receptor molecules and is located on chromosome Xq21.2/Yp11.2. The cadherins facilitate cell signaling and Ca^{2+}-dependent cell adhesion, which is important for development of the CNS (88). Carrasquillo *et al* (89) revealed that genetic variation in PCDH11X was strongly associated with LOAD susceptibility. The authors found that SNP rs5984894 on Xq21.3 in *PCDH11X* was strongly associated with LOAD in individuals of European descent from the USA. PCDH11X is highly expressed in the cerebral cortex and hippocampus. Furthermore, *PCDH11X* is considered as a good candidate gene for PSEN-dependent processing and neurodegeneration (90).

4. Other susceptible genes of AD

Hemochromatosis (HFE). The *HFE* gene is located on chromosome 6p21.3 and it functions to regulate iron absorption. Iron imbalance may affect plaque formation and amyloid processing. Thus, loss of iron homeostasis can be central to the pathogenic events in AD (91). Furthermore, iron is important in the pathology of AD; thus, genetic factors that contribute to iron deposition resulting in tissue damage may exacerbate AD (92). Mutation of the *HFE* gene increases the risk of AD (93,94). Lehmann *et al* (95) revealed that iron overload may be a causative factor in the development of AD.

Bleomycin hydrolase (BLMH). BLMH is located on chromosome 17q11.2 and is vital in homocysteine-thiolactone metabolism, AD pathogenesis and antigen presentation (96). *BLMH* participates in homocysteine metabolism and homocysteine is a risk factor for AD. Recently, Suszyńska-Zajczyk *et al* (97) revealed that BLMH is key in cytoskeleton dynamics, maintains synaptic plasticity, and inactivation of the *BLMH* gene may be associated with AD.

Myeloperoxidase (MPO). MPO is abundant in Aβ plaques in the AD brain and has potent antimicrobial oxidizing abilities (98). MPO may enhance macrophage generation and the expression levels of proinflammatory cytokines (98,99). Maki *et al* (99) demonstrated that lipid peroxide produced by MPO radical may lead to memory loss, neuronal dysfunction and AD. In addition, a study by Tzikas *et al* (100) demonstrated a possible association of MPO with the plasma Aβ 1-42/1-40 ratio and the authors concluded that elevated plasma levels of MPO may be associated with AD pathogenesis.

Cystatin C (CST3). CST3 is located on chromosome 20p11.21 and is expressed by neurons, astrocytes and microglial cells in the brain. CST3 is involved in neuronal degeneration, but recent data showed that CST3 may exert protective effects in AD by induction of autophagy and proliferation, and inhibition of Aβ aggregation (101). A previous study identified that AD patients have low CSF levels of CST3 when compared with control subjects (102). CST3 polymorphism is associated with AD (103). In addition, CST3 exerts a protective effect in AD by preventing the formation of toxic forms of Aβ (104). A previous study with transgenic mice demonstrated the association of CST3 with non-toxic forms of Aβ and prevention of Aβ plaque formation (105). In addition, the authors revealed that reduced levels of CST3 may impair the neuronal ability to prevent neurodegeneration in AD (105). Recently, Butler *et al* (106) found that a missense variant in *CST3* rs1064039 was associated with age-associated macular degeneration and AD.

Microtubule-associated protein tau (MAPT). The *MAPT* (microtubule-associated protein tau) gene is located on chromosome 17q21.1 and is predominantly expressed in neurons. MAPT functions in axonal transport, assembly and stabilization of microtubules. NFTs in AD are primarily due to hyperphosphorylation of MAPT (107). Furthermore, tau is phosphorylated by protein kinases, such as glycogen synthase kinase 3 and cyclin-dependent kinase 5 (107,108). A previous study demonstrated that the MAPT H1c sub haplotype was associated with LOAD risk (108).

β-site APP-cleaving enzyme 1 (BACE1). BACE1, also termed ASP2, is the enzyme responsible for initiating Aβ generation. γ-secretase and BACE1 are required for the generation of Aβ by the processing of APP (109). A previous study demonstrated that BACE1 activity is increased in AD brains (110). Recently, Cheng *et al* (111) demonstrated that BACE1 enzymatic activity increased in mild cognitive impairment (MCI) and may be responsible for the development of MCI into AD. In an experiment with APP transgenic mouse, knockdown of either BACE or BASE1-antisense transcript (BACE1-AS) homologs caused concordant downregulation of BACE or BACE1-AS homolog, which was followed by a reduction in insoluble Aβ production and Aβ aggregation, and normalization of markers of adult neurogenesis (112).

Collagen XXVα1 (COL25A1). COL25A1 is located on chromosome 4q25 and is collagenous type II transmembrane protein purified from senile plaques of AD brains. In a Swedish population, COL25A1 was associated with increased AD risk (113). In an experiment with mice, overexpression of COL25A1 was associated with Aβ accumulation and increased BACE1 levels, as well as loss of synaptophysin, astrocyte activation and behavioral abnormalities, these finding indicated that COL25A1 may be involved in the pathogenesis of AD (114).Previously, Li *et al* (115) identified that COL25A1 was associated with antisocial personality disorder and substance dependence.

Caspase-1 (CASP1). CASP1 is located on chromosome 11q23 and encodes a protein, which is a member of the cysteine-aspartic acid protease family. CASP1 regulates inflammatory processes by activation of proinflammatory cytokines, such as interleukin (IL)-1β (IL1B), IL-18 and IL-33 precursor proteins, and it regulates the proteins involved in tissue repair and cytoprotection (116).Heneka *et al* (117) revealed that CASP1 is expressed in human mild cognitive impairment and brains of patients with AD. Furthermore, CASP1-derived inflammatory mediators were involved in mediating synaptic dysfunction and cognitive impairment. The role of NACHT, LRR and PYD domains-containing protein 3 inflammasome in the Aβ-mediated inflammatory process indicated that CASP1 may be involved in AD pathogenesis (117).

Cytochrome P450 family 2 subfamily D member 6 (CYP2D6). CYP2D6 is located on chromosome 22q13.1 and encodes a member of the cytochrome P450 superfamily of enzymes. The hepatic cytochrome P450 system is responsible for catalyzing various reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. APOE may influence CYP2D6-associated enzyme and drug metabolism by modifying hepatic steatosis and transaminase activity in the liver (118). CYP2D6 was closely associated with the dopamine transporter and rat brain-specific CYP2D18 has been implicated in dopamine metabolism (119). Pilotto *et al* (120) demonstrated that, in patients with mild to moderate AD, SNP rs1080985 in CYP2D6 may influence the clinical efficacy of donepezil. Whereas, Liu *et al* (121) found no significant association between rs1080985 SNP in *CYP2D6* and common APOE polymorphisms in a Chinese population.

Galanin (GAL). The neuropeptide, GAL is located on chromosome 11q13.3 and regulates cognitive behaviors. GAL inhibits cholinergic neurotransmission and *GAL* overexpression enhances AD progression (122). Overexpression of GAL in transgenic mice was associated with cognitive deficit, suggesting that increased expression levels of GAL may lead to neurochemical and cognitive impairments similar to those in AD (123).

Basigin (BSG). BSG (also termed CD147) is a member of the immunoglobulin super family, which is important in fetal, neuronal, lymphocyte and extracellular matrix development. Zhou *et al* (124) revealed CD147 as a regulatory component of the γ-secretase complex. Furthermore, depletion of CD147 by RNA interference was associated with increased Aβ production, indicating that the presence of the CD147 subunit within the γ-secretase complex decreased the production of Aβ-peptides (124).

5. Conclusion

AD is the most common neurodegenerative disease and is widely recognized as a global challenge for society and health-care providers. EOAD is inherited via an autosomal dominant pattern and predominantly governed by three rare mutation genes as follows: APP, PSEN1, and PSEN2, through a common mechanism of altered Aβ production. In addition, APOE has been recognized as a major genetic risk factor for LOAD. Furthermore, various genes have been implicated in LOAD; these genes primarily mediate the Aβ level, while certain genes are implicated in the metabolic pathway and neuroinflammation. Further studies are required to unravel the complete picture of genetics behind this devastating disease and to provide insight into novel therapeutic targets.

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