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INVOLVEMENT OF GENES IN ALZHEIMER'S DISEASE: OUTLINE AND CONTEMPORARY PERSPECTIVE

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Abstract

Alzheimer's disease (AD) is an irreversible, progressive and neurodegenerative brain disorder characterized by memory impairment that results problems in day-to-day life and in accomplishing usual tasks, causes inconvenience in understanding visual images and spatial relationships. Familial AD is correlated with the mutations in the amyloid precursor protein (APP) and presenilin genes (PSEN1 and PSEN2) and Aβ metabolism, whereas APOEε4 moderates amyloid-related memory decline in preclinical AD. On the contrary, sporadic AD is found to exist with complex interaction of both genetic and environmental risk factors. Genome-wide association studies and whole-exome and whole-genome sequencing have brought out more than 20 loci correlated with AD risk. Genome-wide associated studies (GWAS) have identified polymorphisms in or near several genes that are correlated with AD risk, including ABCA7, CLU, CR1, CD33, CD2AP, EPHA1, BIN1, PICALM and MS4A. Among most of them, central role of ApoE, CLU and ABCA7 in cholesterol metabolism imposes this pathway in AD pathogenesis. CR1, CD33, MS4A, CLU, ABCA7, EPHA1 and TREM2 are associated with neuroinflammation and dysregulation of the immune response. Genes associated with endocytosis and synaptic function are recognized in several GWAS of LOAD risk, including BIN1, PICALM, CD2AP, EPHA1 and SORL1.

Keywords: *Alzheimer's Disease, APOE, Amyloid Precursor Protein, Genes, Genome-Wide Association Studies.*

Introduction

Alzheimer's disease is one of the most common neurodegenerative brain disease which is the most prevalent cause of dementia [1-2]. It is a multifactorial brain disorder with insidious onset and progressive impairment of episodic memory resulting from the coordination of genetic, environmental and lifestyle factors [3-4]. Neuropathological characteristics of AD which provide complete apprehension of the molecular pathogenesis of the hallmarks of the disease are the extracellular accumulation of amyloid beta (Aβ) in plaques composed of amyloid β (Aβ) and the deposition of hyperphosphorylated tau proteins containing paired helical filaments in neurons named neurofibrillary tangles (NFTs) [5-6]. The symptoms of this slowly progressive disease include visuospatial dysfunction, visuoperceptual dysfunction, dyspraxia, executive dysfunction, literacy problems, and language dusfunction, apraxia, aphasia and agnosia conjointly linked with general cognitive symptoms, such as impaired judgment, decision-making, and orientation [7-12].Familial Alzheimer's disease is an uncommon autosomal dominant disease which is correlated with the mutations in the amyloid precursor protein (APP) and presenilin genes (PSEN1 and PSEN2) and Aβ metabolism with onset before age 65 years. On the contrary, sporadic Alzheimer's disease is occurred frequently by ageing in concert with a complex interaction of both genetic and environmental risk factors affecting more than 15 million people worldwide .But, the exact reason of the sporadic form of the disease is unrecognized, probably because of its heterogeneous characteristics [13]. This present article reviews the genetic architecture of Alzheimer's disease with recent advancement of various genotypes with their clinical implications for expanding the genetic roadmap of this disease. This knowledge helps to disclose the possible new drug candidate targets by understanding the pathophysiological mechanisms for early-onset AD (EOAD) and late-onset AD (LOAD).

Genetic details of Alzheimer's disease

Numerous variants of genes involving in Alzheimer's disease risk are shown in figure-1 where APP, ABCA7,CLU play central role on cholesterol metabolism, MS4A, EPHA1, TREM2, CD33, CR1 act on immune response, as well as PICLAM, BIN1, SORL1, CD2AP provide action on endocytes [18].

1. Apolipoprotein E (APOE)

Apolipoprotein E (APOE) is one of the strongest heritable risk factors for late onset of AD which is the essential brain apolipoprotein & secreted by astrocytes [14-17]. The relationship between APOE & AD was first introduced in 1991 [18] and later, it was affirmed in 1993 through studies of an association between the APOEε4 allele and AD risk [19-20]. In addition, apolipoprotein E (APOE) is located on the proximal long arm of 19th chromosome i.e., at chromosome 19q13.2 encoding a pleiotropic glycoprotein [17, 20]. APOE is highly distributed in liver, brain, and macrophages. Again, the concentrations of apoE in plasma and cerebrospinal fluid (CSF) are approximated to be 40–70mg/mL and 3–5mg/mL respectively [21-23]. APOE has two structural domains including the N-terminal domain which has receptor-binding region (residues 136–150), and the C-terminal domain containing the lipid-binding region (residues 244–272); they are joined by a hinge region [24]. On the other hand, single nucleotide polymorphisms rs429358 and rs7412 occur at exon 4 in the APOE gene which has become non-synonymous resulting in an amino acid change from Cys to Arg and Arg to Cys [25]. In humans, based on two amino acid residues (112 and 158), the APOE gene exists as three polymorphic alleles (ε2, ε3, and ε4), where the APOEε3 allele is the most common (77%) and ε2 allele being the least common (8%) [21, 26-27]. Moreover, individuals carrying the ε4 allele have higher risk of AD compared to subjects carrying the more common ε3 allele, whereas the ε2 allele decreases risk [28-29]. APOEε4 increases risk in familial and sporadic early- and late-onset AD by enhancing 3-fold for heterozygous carriers and 8- to 10-fold for homozygous carriers. As a result, an elevated risk in familial and sporadic early- and late-onset AD has been occurred [30] with dose-dependent effect on age at onset [9-10, 30]. Surprisingly, APOEε2 decreases risk for late-onset AD and delays age at onset [9-10, 30]. Homozygous ε2/2, ε3/3, ε4/4 & heterozygous ε3/2, ε4/2, ε4/3 are six types of ApoE phenotypes of allelic variants of ApoE ε2, ε3, ε4 [31]. Rare coding variants that affect risk for AD may also occur in APOE [32-33]; however, deep sequencing of the APOE gene in large data sets has not been carried out [4]. ApoE3 and apoE2 are associated with high-density lipoproteins (HDL) and apoE4 is related to very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) [34-35].

The identification of APOE protein structure of each isoform suggests the correlation between the structure of APOE and the distinct function of APOE isomers in AD [36]. The principle function of APOE is to channelize lipids and cholesterols throughout the body [2, 16, 26, 37-38]. As APOE is a ligand for low density lipoprotein (LDL) receptors, it mediates the binding, internalization, and catabolism of lipoproteins in cell [16, 29, 37, 39-41]. APOE has also been implicated in synaptogenesis, synaptic plasticity, and neuroinflammation [15-16, 37, 39, 41]. It has also role in glucose metabolism, lipolytic enzyme activation and several mitochondrial function [24, 29, 41]. In AD, ApoE binds to extra-cellular SP [24, 42] and intracellular neurofibrillary tangles [41, 43], as well as through Aβ-dependent and Aβ-independent neuropathogenic pathways [19] it affects AD pathophysiology. In the CSF, ApoE/Aβ levels were noticed to be lower in patients with AD than in healthy controls on account of binding of ApoE to the major constituent of senile plaques named Aβ peptide [18, 43].

APOE influences the clearance of soluble Aβ and the Aβ aggregation in the brain by binding to Aβ, where APOE4 binds to Aβ more rapidly than APOE3 and accelerates fibril formation [40, 44-46]. APOE interacts with receptors such as with low-density lipo-protein receptor-related protein 1 receptors (LRP1) and indirectly regulates Aβ metabolism [46-47]. In APP transgenic mice, the amount and structure of intraparenchymal Aβ deposits are altered by APOE in an isoform-specific manner [48-49], whereas APOEε4 carriers exhibit accelerated and more abundant Aβ deposition than APOEε4-negative individuals [50-52]. Neuropathologic and neuroimaging studies demonstrate the association of APOE genotype with cerebrospinalfluid Aβ42 and tau levels [52-54]. A recent study of employed genomic convergence and network analysis approaches that the circulating ApoE level is considered as a potential biomarker for AD [55]. In M.W. Lutz et al, this study evaluated the correlation of age, APOE genotype, and translocase of outer mitochondrial membrane 40 homolog (TOMM40) genotypes & comparative relationship of cerebrospinal fluid (CSF) biomarkers, neuroimaging, as well as neurocognitive tests using data from two independent AD cohorts by using the performance of genetics-based biomarker risk algorithm (GBRA). Here, the GBRA "high" and "low" AD-risk are classified & associated with pathologic CSF biomarker levels, positronemission tomography amyloid burden, and neurocognitive scores. As, the positive predictive values and negative predictive values of the GBRA are found in the range of 70%–80%, the comparison of the performance of GBRA with CSF and imaging biomarkers becomes significant (functional magnetic resonance imaging) [56]. In Y.Y. Lim et al., Aβ positivity coupled with APOEε4 was related with moderately increased decline in memory over a 54-month assessment period. It also suggests that in the preclinical stages of AD, the manifestation of memory decline in older adults with high Aβ is aggravated in the presence of APOEε4 [57].

Cross-sectional studies with appropriate sample sizes (e.g., n>200) suggests that there is no cognitive impairment in APP individuals irrespective of whether they carry ε4 or not [58-63].

Various cross-sectional studies have suggested that the APOEε4 carrying AD patients have greater impairment in memory and executive function than who do not carry APOEε4 or healthy volunteers [64]. In addition, mixed results with AD, APOEε4 carriers have been reported from various longitudinal studies that AD APOEε4 carriers shows slower [65-66], faster [67-69],or equivalent[70-71] rates of cognitive decline than their non-APOEε4 counterparts.

A study was conducted in the Gazi University, Dept. of Neurology to impose the relationship between AD & APOE phenotype & vascular risk factors among 44 patients diagnosed with 'possible AD' and 51 volunteers without an intracranial degenerative disorder included as control group. Here, low education level, smoking, hyperlipidemia, higher serum total cholesterol levels, and hyperhomocysteinemia were reported significantly more frequent in the Alzheimer's Disease group in comparison to the Control Group, due to the presence of apoEε4/ε4 genotypes in the AD group. ApoE4 allele may be responsible for increasing vascular risk factors as well as to affect AD directly [31].

2. APP

β-amyloid precursor protein (APP) is a type-1 transmembrane neuronal protein which appears like a signal-transduction receptor [72]. In addition, it is manifested in many tissues and intensified in the synapses of neurons [72].Again, the encryption of the Aβ peptide precursor occurs in APP gene

which is situated at chromosome 21q21 [73-76]. This recommendation was affirmed with the relationship of specific mutations in APP with EOAD in families [77-80]. Comprising of 19 exons APP gene extends approximately 240 kilobases of DNA whereas full-length APP develops in the Golgi and endoplasmic reticulum [81].

As APP is interlaced to create three transcripts: APP695, APP751, and APP770, at least eight isoforms are produced by alternate splicing of exons 1–13, 13a, and 14–18. These transcripts develop a multi domain protein with a single membrane-spanning region differing from each other [82-84]. Moreover, the APP695 isoform (exons 1–6, 9–18) is the leading APP isoform which is evinced in neurons, whereas the APP751 isoform (exons 1–7, 9–18) is highly showed in astrocytes [85-87]. APP751 and APP770 (exons 1–18) are distinguished from APP695 in that they contain exon seven encoding a serine protease inhibitor domain [81]. At first, APP is made in the endoplasmic reticulum, then post transcriptionally altered in the Golgi (N- and O-linked glycosylation, sulfation, and phosphorylation). Finally, it is released to the cell surface via the secretory pathway, as well as endocytosed and processed in the endosomal–lysosomal pathway from the cell surface [88-89]. As, APP and its by-product Aβ have been noticed to be transferred inside mitochondria, they are involved in mitochondrial dysfunction [90-92]. Its primary function is unknown, though it has been found to be involved in neural plasticity [93] and acts as a regulator of synapse formation. [94]. However, full-length APP is proteolytically processed to yield various fragments via the amyloidogenic and the nonpathogenic pathways. In amyloidogenic pathway, APP can be split by sequential functions of β- and γ-secretases to produce Aβ peptides, secreted amyloid precursor protein-β(sAPPβ) and β-C-terminal fragment (β-CTF). Being encoded by exons 16 and 17 and 39 to 42 amino acids in length at intracellular sites such as the endoplasmic reticulum and Golgi apparatus, extracellularly released Aβ peptides form the extracellular plaques as stylemarks of AD. Simply, APP is split by the β-secretase, named β-site amyloid precursor protein-cleaving enzyme 1 (BACE-1) by producing N-terminal sAPPβ and C-terminal C99 peptide which is cleaved by γ-secretases to produce Aβ [72, 95].

In nonpathogenic pathway, APP is proteolyzed by α- and γ-secretases within abdomen resulting the cleavage of APP. Here, APP is cleft by the action of α-secretase and releases the extracellular amino-terminus of APP as a secreted amyloid precursor protein-α (sAPPα), as well as by the action of γ-secretase, an 83-residue carboxy-terminal fragment (C83) is generated by releasing extracellular p3. In addition, the intracellular cytoplasmic fragment is identified as amyloid intracellular domain (AICD) to show neurotrophic and neuroprotective activities [72, 95-98]. The product C-terminal fragments are of 10 and 12 kDa, respectively, which are entered into the membrane and accumulated in the brain [99]. It has been found that collection of APP C-terminal fragments (CTFs, C83, C89, and C99) especially C99, may act as neurotoxic by itself where APP CTFs are able to provide synaptic plasticity and long-term memory in murine models of AD [100-105].

In Goate et al. (1991), the accumulation of a missense mutation of APP was found first in families with AD and subsequently found that two mutations including a single amino acid substitution (Phe for Val) in the transmembrane domain and a Val for Gly substitution at codon717 [78,80] had been occurred. From another study, the mutation was found to exist in exon 17 of the APP gene which was partially encoded for the Aβ peptide resulting a valine to isoleucine change at amino acid 717 (Val717Ile) corresponding to the transmembrane domain of the protein. In numerous recent studies, more than 30 different APP missense mutations have been recognized, among them approximately 25 are pathogenic, in most cases developing in autosomal dominant early-onset AD [106]. Since, numerous APP mutations cluster at or after the C-terminal portion of the abdomen, they change γ-secretase function. They exhibit an alteration in APP processing that stimulates the highly amyloidogenic Aβ42 fragment and decreases the Ab40 fragment providing an altered Aβ42/Aβ40 ratio without a change in total Aβ levels [107]. Distinct number of APP mutations have been recognized in AD patients, among them 23 are missense mutations, nine duplications, and one deletion [106], whereas majority of the mutations are dominantly inherited and located the *β*-and *γ*-secretase cleavage sites by regulating APP proteolytic processing and aggregation. The Italian mutation (E693K) [108], Dutch mutation (E693Q) [109], Arctic mutation

(E693G) [110], Iowa mutation (D694N) [111], London mutation (V717I) [77-78, 112-113], the V717G [77], V717F [80,113] and V717L [80,113- 117] mutations and E693del mutation [114] have been recognized in APP residues V717 and E693, developing both residues mutation hotspots in the APP gene. Numerous mutations, such as the Iranian mutation (T714A) [115], Australian mutation (T714I) [116], French mutation (V715M) [117], German mutation (V715I) [106], Florida mutation (I716V) [118], frame the other end of the Aβdomain are situated just distal to the C-terminus of the Aβ domain adjacent to the γ-secretase site, whereas other mutations such as the Flemish mutation (A692G) [119] are found to be located within the Aβ coding sequence. In Suzuki et al., three such mutations (V717I, V717F, and V717G) were systematically related with a 1.5- to 1.9-fold increase in the generation of longer beta-amyloid fragments by generating insoluble amyloid fibrils more rapidly than shorter fragments [120]. Yamatsuji and colleagues showed that in cultured neuronal cells expression of the cytoplasmic domain of any of the mutations at amino acid 717 (V717I, V717F, and V717G) accelerated G protein-mediated nucleosomal DNA fragmentation [121].

In recent epoch, Jonsson and colleagues found a rare mutation (A673T) in the APP gene which was found to be protective in contrast to AD leading to an approximately 40% reduction in the production of amyloidogenic peptides in vitro [122]. Mutations in APP genes have become autosomal dominant in most cases, the mutation A673V stimulates AD in an autosomal recessive pattern [123-124]. As, copy number variant mutations are common occurrence in APP [125], down's syndrome (caused by the presence of an extra chromosome 21) produces three copies of APP resulting AD because of abundance of APP [126]. Approximately 14% of early-onset autosomal dominant cases of AD are occurred by dominant mutations in APP [127] and two recessive APP mutations, A673V and E693D, generate early-onset AD [127].

3. Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2)

Presenilins are starring components of the atypical aspartyl protease complexes and these are accountable for the γ-secretase cleavage of APP [128]. In addition, PSEN1 and PSEN2 are integral membrane proteins comprising nine transmembrane domains with a hydrophilic intracellular loop region. They are situated at chromosome 14q24.3 and 1q31-q42 respectively [129-130] and form catalytic core of the γ-secretase complex. They are observed at the cell surface, but they may also be located in the Golgi, endoplasmic reticulum and mitochondria [131-134]. However, PSEN1 is composed of 12 exons encoding a 467-amino-acid protein which is anticipated to traverse the membrane 6 to 10 times; the amino and carboxyl termini are both pointed toward the cytoplasm [135].On the other hand, PSEN2 is composed of 12 exons and formed into 10 translated exons encoding a 448-amino-acid peptide, as well as is recognized by sequence homology [136-140]. Again, more than 185 mutations in PSEN1 have been introduced [30,130] as the most familiar cause of early-onset AD and accountable for 18–50% of autosomal dominantearly-onset AD [134], as well as most of them is missense mutations responsible for amino acid substitutions. Although, mutations in PSEN1 develop the most severe forms of AD with complete penetrance; onset becomes apperant at approximately 58 years of age with the exhibition of incomplete penetrance [141]. Numerous studies have been conducted with various types of PSEN-1 mutations in different ethnic groups where founder mutation in PSEN1 was found to develop early-onset AD in unrelated Caribbean Hispanic families [142].

Yescas et al. (2006) reported that in Mexican families, AD was developed by the A431E mutation. An unusual onset age in adolescence was reported by PSEN1 L166P mutation, where in vitro studies introduced that this mutation stimulated exceptionally high levels of Aβ42 production by impairing Notch signaling [143-144].

A retrospective cohort study engaging 449 participants, who were PSEN1 E280A carriers having complete clinical follow-up reported distinct stages of clinical progression to AD dementia. The study introduced asymptomatic pre-mild cognitive impairment (pre-MCI), symptomatic pre-MCI, MCI, dementia, and death were developed at approximately 35 years, 38 years, 44 years, 49 years and 59 years of age, respectively [145]. 13 dominant, pathogenic PSEN2 mutations are responsible for approximately 5% of early-onset, familial AD cases [30].Missense mutations in the PSEN2 gene have been reported that the age of onset of AD patients are highly variable and lower penetrance than PSEN1 among affected family members, whereas the activities of PSEN2 in early-onset AD remains unidentified [146]. A

recent study reported that mutant PSEN2 stimulates the action of β-secretase by regulating reactive oxygen species-dependent activation of extracellular signal regulated kinase [147]. Recent evidence suggests that numerous nonpathogenic or unknown pathogenic additional variants, such as PSEN2 R62H [148] and PSEN1 E318G [149] are identified and supposed to act as risk factors for AD.

The γ-secretase complex is formed by comprising PSEN1 ,PSEN2 ,nicastrin, anterior pharynx-defective-1 (APH-1), and presenilin enhancer 2 (PEN2) by catalyzing the cleavage of many membrane proteins [150]. Kinetic reports by Cha´vez-Gutie´rrez and colleagues have exhibited that familial AD mutations in PSEN1 and PSEN2 alter the action of γ-secretase by three mechanisms [151]. First, the intracellular domain of APP is released by the variable inhibitory action on the initial endoproteolytic cleavage step. Second, the premature release of Intermediary substrates of APP occurs during the consecutive carboxypeptidase-like γ-secretase cleavage resulting the generation of longer Aβ peptides. Finally, the cleavage of APP at position 49–50 or 50–51 has occurred by the action on the cleavage site .These three mechanisms present a demonstration of the historical facts that PSEN1 and PSEN2 mutations occurs with the alteration of Ab42/Ab40 ratios.

4. ATP Binding Cassette Transporter 7 (ABCA7)

ATP-binding cassette transporter A7 (ABCA7) belongs to the ABC transporter superfamily which is is a 2,146-amino acid protein having two highly conserved ATP binding cassettes [152-153]. The location of ABCA7 which was first recognized in macrophages is on chromosome 19p13.3 encoding a protein with suspected roles in lipid metabolism and the phagocytosis of apoptotic cells [152, 154-155]. Having 46 Exons, it spans about 32kb [152-154], whereas the mRNA is 6.8kb In length encoding a polypeptide of 2146 amino acids with a calculated molecular weight of 220kDa [152]. ABCA7 has spliced into two transcripts, both of which are expressed in the brain [156]. But it is distributed abundantly in myeloid cells, particularly monocytes and granulocytes [152]. Here, expression is stimulated by distinction of monocytes into macrophages [152] whereas in macrophages, up-regulation of both mRNA and protein is occurred through altered low-density lipoprotein and down-regulation is reported in presence of HDL [152]. Again, ABCA7 is distributed in hippocampal CA1 neurons where its expression occurs at 10-fold higher levels in microglia [156].Various SNPs of ABCA7 were recognized by GWAS in LOAD as risk alleles, whereas rs3764650 [157-160] and rs4147929, which were recognized in a meta-analysis of 74,046 individuals [160]. LOAD risk is stimulated through polymorphisms in this region. But, the impact of these polymorphisms on ABCA7 function and in AD is poorly recognized through various observations [161-162]. In brains with AD, rs3764650 in ABCA7 is linked with neuritic plaque burden [163]. A behavioral study of ABCA7 knockout mouse model reported that ABCA7 mRNA expression in autopsy brain tissue is also correlated with advanced cognitive decline [161-162]. ABCA7 acts as key regulator in the efflux of lipids from cells into lipoprotein particles whereas in vitro, ABCA7 enhances cholesterol efflux by inhibiting Aβ secretion [164-165].Through the C1q complement pathway, ABCA7 has been reported to mediate phagocytosis of apoptotic cells by macrophages [166].Stimulated levels of ABCA7 increases microglial phagocytosis of apoptotic cells, synthetic sub-strates, and Aβ [164,166-168] and also enhances AD risk by cholesterol transfer to APOE or by clearing Aβ aggregates [164-165,169]. ABCA7-deficient mice have been reported to show only modest effects on lipid homeostasis in comparison with ABCA1-deficient mice [164,170], suggesting that ABCA7 is not essential.

5. Bridging Integrator 1(BIN1)

The BIN1 (Bridge Integrator 1 or Amphiphysin 2) is a widely evinced 70 kDa nuclear protein whose location is on chromosome 2 (2q14.3) encoding several splice variants [171-173]. Being differentially spliced to seven major transcripts, it is mostly distributed in the brain and the muscles and has 20 exons [172,174-175]. All of these are ascertained by immune precipitation and immune fluorescence experiments [173]. Previously it was recognized as Myc box-dependent-interacting protein 1 which interacts with Myc-box regions of the MYC oncoprotein [173]. The involvement of BIN1 in posterior cortical atrophy has been observed [176]. The relation between the terminal portion of BIN1 and amphiphysin which is a cancer-associated autoantigen, and again to RVS167 which is a popular as a regulator of the cell cycle in yeast is well-establised [173]. The role of BIN1 as tumor suppressor is detected by the negative influence of the cell cycle [173]. 10 isomers of BIN1 have been

identified which are developed by variable splicing of the mRNA [175] among them largest isoform is distributed exclusively in the brain and concentrated in nerve terminals (NCBI GeneID 274; http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene &cmd= Retrieve& dopt=full_report&list_uids=274) and other smaller isoforms are brought forth generated by deletion of downstream exons, particularly 7, 11, 13, and 14 (NCBI Gene ID 274).

The SNPs in BIN1 which are responsible to enhance risk for LOAD were recognized by GWAS [157-158], whereas the most recent LOAD GWAS of 74,046 individuals found out rs6733839 [160]. Among other SNPs, SNP rs7561528 is responsible for entorhinal cortical thickness and temporal pole cortical thickness [177], whereas the SNP rs59335482, in linkage disequilibrium with rs744373, is correlated with upgraded BIN1 mRNA expression and tau loads, but not tangles, in brains with AD [178]. The most significant SNPs, rs744373 and rs7561528, are found to be situated >25 kB upstream from the BIN1 coding region [160]. Two nonsynonymous SNPs in BIN1, rs11554585 (R397C) and rs11554585 (N106D) are anticipated to be deleterious by employing bioinformatics approaches [179]. Being widely distributed in neurons, BIN1 physically interacts with tau in neuroblastoma cells and mouse brains [178], whereas the distribution of BIN1 in frontal lobes of 24 sporadic AD patients is lower in comparison with 24 control patients [180]. These two contradictory phenomenon need to be confirmed by further experiments.

In aging mice, in transgenic mouse models of AD, and in persons with schizophrenia , the variation of the nature of BIN1 has been exhibited [181-182].Amphiphysin 1 (a related protein) knock-out mice show lower synaptic vesicle recycling efficiency, seizures, and cognitive (memory) deficits [183]. In addition, the protein is recognized as the substrate for CDKL5, in which gene can be found to undergo mutation in patients with Genetics of AD 269 West syndrome and Rett syndrome, severe neurodevelopmental disorders [184]. The interaction of BIN1 with another microtubule-associated protein (CLIP-170) has been reported [185]. The suppression of BIN1 knockdown in tau-induced toxicity occurred which was observed in Drosophila model of AD [178]. BIN1 interacting with clathrin and AP2/α-adaptin [186-187] and binding to lipid membranes, BIN1 stimulates membrane curvature [188]. The role of BIN1 is in modulating clathrin-mediated endocytosis, intracellular endosome trafficking, senescence, immune response, calcium homeostasis, and caspase-independent apoptosis [95,174, 189, 191,192]. On the other hand, BIN1 has been shown to involve in phagocytosis by macrophages and binds α-integrins to govern the immune response [190].

Overall key functions of BIN1 is endocytosis and membrane recycling, cytoskeleton regulation, DNA repair, cell cycle progression, and apoptosis and decreased expression related with centronuclear myopathy, cardiomyopathy, and cancer [193] whereas upgraded expression is reported in AD.

6. Clusterin (CLU)

Clusterin (CLU) is a 75-kDa apolipoprotein which is widely distributed throughout the body, especially in the brain by playing a valuable role in apoptosis, complement regulation, lipid transport, membrane protection, and cell-cell interactions [194]. Structurally, the heterodimeric CLU is structurally comprised of two subunits joining by disulfide bonds [195], where subunits are generated by proteolytic cleavage of the clusterin precursor protein into alpha- and beta-peptide fragments [194].The location of CLU is on chromosome 8p21.1 which is a stress-activated chaperone protein encoding three alternative transcripts [194,196]. Because of having two coiled-coil α-helices, clusterin is considered as a heat shock protein [197]. CLU gene consists of 9 exons, covering 16Kb of DNA and is expressed in high sequence homology (70%–80%identity) across mammalian taxa [198]. Numerous single nucleotide polymorphisms (SNPs) have been recognized in CLU providing protection against LOAD, including rs11136000, rs9331888, rs2279590, rs7982, and rs7012010 [157-159,199] where a relationship of CLUrs9331896 with LOAD was studied in 74,046 individuals [160]. But the practical influence of these polymorphisms is poorly unknown. The SNPrs9331888 is connected with expression of an alternative splice variant [44] and rs9331888 and rs11136000 are found to exhibit effects with plasma clusterin levels [200-202]. Stimulated clusterin plasma levels are also related with brain atrophy, disease severity, and disease progression [203-204], whereas Clusterin messenger RNA (mRNA) expression is stimulated in brains with AD being recognized in amyloid plaques [161,205-207]. As, clusterin alters Aβ clearance, amyloid deposition, and neuritic toxicity, purified clusterin interacts

with Aβ affecting fibril formation in vitro [208-209]. By influencing the membrane attack complex, clusterin inhibits the inflammatory response associated with complement activation [194]. Since neuroinflammation is a stylemark of AD, SNPs that influence clusterin expression or its role as an amyloid response agent could alter AD pathogenesis and downstream effects.

7. Ephrin Type-A Receptor 1 (EPHA1)

EPHA1 belongs to the ephrins family of tyrosine kinase receptors whose location is on chromosome 7q34 encoding the ephrin type-A receptor 1 protein [210] .The EPHA1 attaches to membrane-bound ephrins-A ligands on adjacent cells resulting contact-dependent, bidirectional signaling to adjacent cells [211]. Having 18 exons ,the EPHA1 genes span a little over 18kb[210] ,whereas EPHA1 protein is composed of 976 amino acids which is approximately 108kDa [212]. EPH receptors regulate the MAPK pathway and response at glutamatergic synapses [212-214]. However, in transgenic mouse models of AD, it was reported that ephrin receptors were lowered in the hippocampus prior to the development of impaired object recognition and spatial memory ,whereas low levels of Eph receptor have been detected in postmortem hippocampal tissue from patients with incipient AD [215]. Depending upon the nature of the ligand, the family is divided into two groups. Between them, EPHA receptors attach to GPI-anchoredephrin-A ligands and EPHB receptors attach to ephrin-B proteins which contain a transmembrane and cytoplasmic domain [216].As, this class of proteins have been anticipated to key regulator of a "global positioning system" for developing cells in olfactory, cochlear, retinal and thalamocortical pathways [217] and these family of proteins have been involved in modulating brain development and axonal guidance [218]. It is distributed by CD4-positive T lymphocytes and monocytes [219].The correlation of the SNP rs11767557, near EPHA1 with reduced LOAD risk have been reported [158-159], as well as the SNP rs11771145 was related with reduced LOAD risk in the largest GWAS study [160]. The modification of mRNA expression with EPHA1 in brains with AD has not been reported [161].EPH and ephrin signaling play crucial role in the formation of segmented structures whereas EPH receptors are key regulators in guiding neural plasticity in the adult brain [220].

8. Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM)

PICALM is a 70kDa protein affecting clathrin assembly which is expressed in pre-and postsynaptic structures, as well as it has been involved in the membrane retrieval of the synaptic vesicle [174, 221-222].The location of the PICALM gene is on chromosome 11 (11q14.2) with 23 alternative transcripts having three isoforms. Here, the canonical sequence is 652 amino acids in length and two additional isoforms are made by deletions of short sequences of amino acids near the 3 ends of the transcript. Again, the first 289 amino acids of the protein contain high degree of homology (81%) to the clathrin assembly protein AP3 and participate in clathrin-mediated endocytosis (CME) existing in the plasma membrane [174]. The participation of PICALM in CME is significant in the critical step of the intracellular movement process of lipids and proteins [222] and incorporation process of full-length APP from the cell surface in cell culture studies [223].

Being distributed in neurons, PICALM colocalized with APP in endocytic vesicles [224]. Moreover, it formed a complex which could be introduced by autophagosomes and target vesicles containing APP [225] and indicates a significant role in Aβ clearance. Again, colocation of PICALM with APP occurs in vitro and in vivo where APP trafficking is changed in vitro, and overexpression of PICALM in vivo stimulates plaque deposition in AD transgenic mice [224]. Another study showed that cleaved fragments of PICALM were reported to be enhanced in AD (LOAD and EOAD) brains contrasting to controls where expression was demonstrated in neurons, microglia, and colocalized with neurofibrillary tangles only, and no colocalization with aggregated Aβ was detected [226]. Aβ-induced toxicity in a yeast model is stimulated by PICALM [227]. The PICALM gene was first recognized in studies of myelogenous leukemia being the fusion partner of AF10 in a chromosomal translocation which is expressed in acute myeloid leukemia, acute lymphoblastic leukemia, and malignant lymphoma (10;11)(p13;q14) [228].Meyerholz and colleagues have reported that PICALM is connected with the alpha-appendage domain of the AP2 adaptor through the three peptide motifs 420DPF, 375DIF, and 489FESVF showing less effect with the amino-terminal domain of the clathrin heavy chain [229]. The levels of PICALM were enhanced in the brain

of an amyloid mouse model of AD in contrast to wild-type mice [230].Although In the PICALM gene, Schnetz-Boutaud et al. (2012) became unable to introduce new variants after sequencing the gene in 48 cases and 48 controls, it was found that a previously described splice variant in LD with the GWAS hit could develop a causal function [231].Ferrari et al. (2012) introduced several rare coding variants in the PICALM regions, among them none was correlated with risk of AD [232].The relationship of reduced LOAD risk with the SNPs 5' to PICALM rs3851179 and rs541458 is introduced [157,160,199]. In a study of predicted pathogenicity of nonsynonymous SNPs in PICALM, one SNP, rs12800974 (T158P) is supposed to show deleterious effect [179]. PICALM-deficient mice do not show any neurologic activities whereas mice exhibiting nonsense point mutations in the PICALM gene have implicated in abnormal hematopoiesis and iron metabolism involving in APP processing [233]. PICALM alters synaptic vesicle fusion to the presynaptic membrane through VAMP2 trafficking [221] whereas impaired clathrin-mediated endocytosis is observed with the deletion of the PICALM homolog AP180 in Drosophila and yeast [234-235].PICALM inscribes clathrin and adaptor protein complex 2 (AP2) to the cell membrane by providing valuable function in the determination of the amount of membrane which may be recycled to influence clathrin cage size [236].

9. SORL1

Sortilin-related receptor L (SORL1) belongs to member of the Vsp10p domain receptor family which is located on chromosome 11q23.2 encoding a 2,186-amino acid polypeptide [237]. In addition, SORL1 contains homology to the RAP binding receptor gp95/sortilin [238] implicated in vesicle trafficking from the cell surface to the Golgi-endoplasmic reticulum [237]. There is also evidence that SORL1 plays crucial role for the processing of APP by presenilins and the production of beta-amyloid [239]. Being composed of five type I transmembrane receptors, SORL1 was originally introduced as an AD risk gene in candidate-based approaches [237,240]. It binds lipoproteins, including APOE-containing particles for modulating their uptake through endocytotic pathways [237].Again, SORL1 attaches to lipoproteins, including APOE-containing particles for altering their uptake by endocytotic pathways [237]. Recent meta-analysis of one observation has been reported a significant link between clusters of polymorphisms in SORL1 and AD in both Caucasians and Asians [241]. A GWAS in 74,046 individuals has shown that rs11218343 near SORL1 is linked with decreased levels of AD risk [199].On the other hand, SORL1-deficient mice have been reported to contain elevated Aβ levels [242], whereas SORL1 mRNA expression is shown to provide reduced labels of risk in brains with AD [242-244].

10. Tau

Tau is a phosphoprotein with starring activity in the stabilization of microtubules, exhibiting vital roles for cytoskeletal support and intracellular transport of organelles, secretory vesicles, and other substances such as neurotransmitters. The location of the microtubule-associated protein tau gene (MAPT) is on chromosome 17 of the human genome which is expressed as six isoforms of the tau protein in adult human brain (central nervous system; CNS), but not in the peripheral nervous system (PNS) [245- 246]. These isoforms develop from the alternative splicing of exons 2, 3, and 10 of the 16 exons within MAPT, whereas exons 2 and 3 express a 29- and 58-amino acid sequence, respectively, as well as exon 10 expresses an additional microtubule-binding domain resulting zero, one, or two N-terminal repeats and three or four C-terminal microtubule-binding domains (3R or 4R tau) [246]. The longest (2N4R) and shortest (0N3R) isoform is composed of 441 and 352 amino acids, respectively as well as the N-terminal projection domain of tau (2N4R) is composed of a 44-amino acid glycine-rich sequence and residues 45–102 encompass two highly acidic regions (N1 and N2-domains) [247-248]. Simply, tau is the cardinal constituent of neurofibrillary tangles, which are distributed in copious in neurons of the central nervous system (CNS) but are also distributed at very low levels in CNS astrocytes and oligodendrocytes predicting of high AD progression [249].

More than 30 mutations of tau in the chromosome have been verified, among them 17 have been recognized in frontotemporal dementia, linked with Parkinson's disease [250] .However, the correlations between tau mutations with AD are poorly understood. Nevertheless, induced levels of both phosphorylated and total tau in the CSF link up with reductions in scores on cognitive examinations [251]. Being phosphorylated, tau proteins result defective and no longer stabilized

microtubules. In addition, hyperphosphorylated tau becomes insoluble exhibiting lack of affinity for microtubules and self-correlation into paired helical filament structures [252-253]. Again, the Drosophila orthologs to CD2AP, FERMT2, and CELF1 were introduced as key regulators of tau-mediated toxicity [163]. Being cytotoxic [254], aggregates of abnormal tau molecules impair cognition [255, 256]. However, tau has been correlated with induced oxidative stress, impaired protein-folding function in the endoplasmic reticulum, and deficient proteasome-mediated which is also linked with autophage-mediated clearance of damaged proteins in AD [257-258]. The elevated levels of phospho-tau amino acids (T181, T231) and total tau in the CSF are shown to represent a biomarker test with good accuracy to predict incipient AD in patients with mild cognitive impairment [259]. Double mutant (tau/APP) transgenic mice demonstrated a neurofibrillary tangle pathology which was substantially induced in the limbic system and olfactory cortex [260]. Moreover, Aβ-elevated degeneration of cultured neurons and cognitive deficits, which are well-known as typical symptoms of AD in experimental models, need the presence of endogenous tau [261-262]. Number of neurofibrillary tangles in cell bodies are induced a five-fold through the injection of Aβ42 into the brains of mutant tau transgenic mice [263]. Recent CSF GWASs have exhibited that APOE genotype generates an Aβ-independent effect on CSF tau levels, indicating that APOE could regulate tau accumulation in the brain [264], while the release of tau from the cell may be altered by synaptic activity [265-268]. Expression of the Drosophila ortholog of BIN1 is attenuated with reduced tau-modulated toxicity in a Drosophila model [269].

11. TREM2

TREM2 is one type of transmembrane receptor protein which is distributed on myeloid cells to regulate phagocytosis and suppress inflammation reactivity [270] including microglia, monocyte-derived dendritic cells, osteoclasts, and bone-marrow-derived macrophages [271]. The location of TREM2 is on chromosome 6q21.1 which has been reported to exist as three transcripts. Among them, the longest transcript is trafficked to the cell surface encoding a transmembrane protein [271].Then, binding with several ligands, it interacts with DAP12 (also known asTYROBP) and intra-cellular signaling through TYROBP is transduced by TREM2. But the natural ligands of TREM2 have to remain speculative, upon ligand binding TREM2 links with TYROBP to alter downstream signaling. Again, the transmembrane domain is observed to be lost from the shorter transcripts. Although these transcripts have not been experimentally recognized, they are anticipated to become mystery [271]. Variants in the TREM2 region are linked with cerebrospinalfluid tau levels [264] whereas after trafficking to the cell surface, TREM2 is split by γ-secretase [272]. Through exome and genome sequencing, an excess of variants in exon 2 of TREM2 was introduced in AD patients. R47H was recognized in GWAS by imputation and further observation after direct genotyping. R47H has been observed to mediate risk of early-onset AD in a French population [273], whereas R47H has been found to be replicated in a Spanish population from the USA [274], a Columbian family study with frontotemporal and AD dementia [275] in the Cache County study [276], in a Spanish/Catalan study [277], a Belgian study [278], and an African-American sample [279]. But, the R47H variant was not recognized in a Chinese population of 1133 cases and 1157 controls and four variants detected in TREM2 were not correlated with LOAD [280]. Bertram, Parrado, and Tanzi (2013) verified the results observed by Jonsson, but with a lower effect size, suggesting a "winner's curse," and shown to the very low population attributable fraction and the inappropriateness of a comparison of the effect size of TREM2 with that of the APOE εallele [281-283]. TREM2 mutation key regulators with AD have more extensive brain atrophy in comparison with noncarriers with AD [284]. The most common variant in populations of European descent, R47H (rs75932628), has recognized to enhance LOAD risk approximately two fold [275, 285-288]. Subsequent studies found that heterozygous and homozygous mutations inTREM2 have been reported to correlate with autosomal recessive forms of dementia with bone cysts and fractures resulting clinically distinct disorders [285,289-291]. Numerous studies have shown that autosomal recessive mutations in TREM2 have been introduced in a family with frontotemporal dementia–like syndrome without bone involvement [30] whereas rare, missense mutations in TREM2 stimulates LOAD risk which is suggested by gene-based burden tests . Another recent study has been shown that TREM2 R47H and TREM2 R62H are correlated with AD risk [278].

12. Phospholipase D3 (PLD3)

PLD3 is defined as nonclassical phospholipase which is situated at chromosome 19q13.2 without any prominent catalytic activity [285]. Although its characteristics are poorly known, it is found to be linked with AD risk splicing into 25 predicted transcripts [292]. PLD3 is highly distributed in neurons in the hippocampus, entorhinal cortex, and frontal cortex. In vitro, coexpression of PLD3 with APP generates significantly reduced extracellular Aβ levels by an unknown mechanism [11], while knockdown of PLD3 results induced levels of Aβ [292]. A correlation between PLD1 and PLD2, classical phospholipases, and APP metabolism has been observed [293-294].Catalyzing the hydrolysis of phosphatidylcholine, classical PLD proteins have been found to generate phosphatidic acid, which performs as a regulator for clathrin-mediated endocytosis resulting the involvement in AD pathogenesis [293- 296].

13. CD33

A key member of the immunoglobulin superfamily called CD33 is positioned on chromosome 19q13.3 [210] by encoding a member of the sialic acid-binding immunoglobulin-like lectins (Siglec) family of receptors, and distributed on myeloid cells and microglia [297-299].CD33 genes span 14.2kb by containing seven exons [300], whereas two mRNA species of 1.4-1.5kb and 1.6–1.8kb have been reported through alternate splicing of the transcript [301]. The length of the CD33 protein is 364 amino acids having a mass of approximately 40kDa [302] which contains two immunoglobulin-like domains, a transmembrane region and acytoplasmic tail that has two potential ITIM sequences [303].Being a member of family of cell-surface receptors, CD33 plays an important role as an adhesion molecule to modulate sialic acid-dependent binding to cells [303-304] whose main function is involved in the peripheral circulation on monocytes and myeloid progenitor cells [128–131,299,305-307]. As, CD33 may act as an inhibitory receptor by colligation with CD64 on myeloid cells [308], sialic acid binding activates CD33, resulting monocyte inhibition through immunoreceptor tyrosine-based inhibitory motif domains [309]. CD33 also modulates clathrin-independent receptor-mediated endocytosis [310] where splicing of CD33 regulates microglial activation [297]. CD33 is normally distributed on the surface of myeloid progenitor cells, mature monocytes, and macrophages, and is involved in inhibition of cell activity where high CD33 brain expression has been correlated with AD status [161,298]. Two isoforms have been identified, between them one contains the seven exons of the genes, and other contains the genes without the second exon encoding the V-set immunoglobin domain which is key regulator for the sialic acid-binding activity [311].CD33 mRNA expression is specifically increased in microglia, and expression in autopsy brain tissue is associated with more advanced cognitive decline [161,298]. Aβ phagocytosis is inhibited in immortalized microglial cells expressing CD33, and this effect is abolished in cells expressing CD33 lacking exon 2 [298]. The minor allele of rs3865444 is associated with reduced CD33 mRNA expression and insoluble Aβ42 in brains with AD [298]. As, CD33-positive immunoreactive microglia have been implicated with insoluble Aβ42 and plaque burden in brains with AD [161] .CD33 may function in Aβclearance and other neuroinflammatory pathways which are regulated by microglia in the brain.The GWAS SNP, rs3865444, was found to be correlated with the surface expression of CD33 on circulating monocytes [312] .In LOAD GWAS, the identified SNPs proximal to CD33(e.g., rs3865444) were observed to lower LOAD risk [158-159, 287] whereas the SNP rs3865444 is related to stimulate CD33 lacking exon 2 [297] and rs12459419 alters exon 2 splicing efficiency [297]. Finally, Malik et al. and Raj et al. detected a correlation between the AD risk allele of rs3865444 and greater expression of the CD33 isoform which carries the Ig V-set domain which could describe the relation with AD [297,313].

14. Complement Receptor 1 (CR1)

Being a member of the receptor of complement activation (RCA) family, Complement receptor 1 (also known as CD35, C3b/C4b receptor) exhibits complement response, as well as it is distributed on phagocytic cells, such as erythrocytes, leukocytes, choroid plexus, microglia, and splenic follicular dendritic cells leading to the ingestion and removal of complement-activated particles [314-315]. In addition, the CR1 protein is a monomeric type I membrane glycoprotein which plays a significant role in optimizing the main system for processing and clearance of complement opsonized immune complexes and modulates cellular binding to particles, those are marked with activated complement [314]. The

location of CR1 is on chromosome 1q32 in a cluster of complement-related proteins and encodes the CR1 protein. CR1 encodes four co-dominant alleles which are different in sizes and undergoes multiple genetic duplication and deletions events [316]. The most common CR1 isoforms are the "F" and "S" allotypes of 250 and 290kDa, respectively where the size difference is based on the inclusion of a long homologous repeat of 40–50kDa [198]. As, CR1 acts as the human receptor for C3b and C4b complement cleavage fragments [317], the relationship of an increased risk of developing late onset Alzheimer's disease with certain alleles of this gene have been statistically developed [199]. On the other hand, CR1 is a negative regulator of the complement cascade acting through immune adherence and phagocytosis, as well as suppressing both the classic and alternative complement pathways [314].

Moreover, in GWAS, SNPs in CR1 were recognized in LOAD [157- 160,199] whereas the connection of variants in the CR1 locus with neuroimaging measures in AD [177] and neuritic plaque burden in brains with AD [163] was observed. The SNP rs6656401 tags several SNPs which are noticeably correlated with AD risk, and a second SNP called rs3818361, is related with LOAD risk in APOEε4 carriers [199]. CR1 mRNA expression in autopsy brain tissue is also correlated with developed cognitive decline [161]. It is shown that CR1 provides high-expression and low-expression alleles [311]. On the other hand, subjects who are homozygous for the low-expression CR1 allele contain 200 copies of CR1 per cell, whereas subjects who are homozygous for the high-expression allele carry nearly 1400 copies per cell [316]. Higher CR1 protein expression is connected with a higher clearance rate of immune complexes [318-319].

Brouwers et al. (2012) and Hazrati et al. (2012) have recognized a sub region of CR1 which carries two SNPs related with risk of AD and with Aβ42 levels in the cerebrospinal fluid. Those signals were likely modulated by a copy number variation (CNV) connected with risk of AD. They mediate levels of two particular isoforms of CR1, CR1-F and CR1-S and the latter carries an extra binding site for C3b/C4b. Binding to Aβ, C3b and C4b could take part in Aβ clearance [320-321]. The level of CR1 is lessened in pathological conditions such as systemic lupus erythematosus (SLE), HIV infection, some hemolytic anemias, and other conditions featuring immune complexes [322,323]. A coding variant of CR1 is related with cognitive decline which was introduced by Keenan et al. (2012) but this observation could not be repeated in a second cohort [324-325].

15. AKAP9: a kinase (PRKA) anchor protein 9

The location of AKAP9 is on chromosome 7q21.2 and distributed in the hippocampus, cerebellum and the cerebral cortex [91]. Logue et al. reported the exhibition of AKAP9 in seven unrelated African-Americans with familial AD, and two rare variants (rs144662445 and rs149979685, with a MAF of 0.43% and 0.36% respectively depending on the Exome Variant Server database (http://evs.gs.washington.edu/EVS))[326]. In addition, in-silico analyses designate that rs144662445 does not contain a greater impact on protein activities depending on predicting algorithms, but rs149979685 could modify the role of the encoded protein. A scaffold protein is encoded by AKAP9 with physical attachment of type I protein phosphatase (PP1) and cAMP-dependent protein kinase (PKA) to the N-methyl-D-aspartate (NMDA) receptors to modulate channel activity [327].

16. CD2 Associated Protein (CD2AP)

CD2-associated protein (CD2AP) is a scaffolding protein which is located on chromosome 6p12 encoding CD2 associated protein [328]. The protein is composed of 639 amino acids having deduced molecular mass of approximately 70kDa [329]. In addition, it plays crucial role in cytoskeletal reorganization and intracellular trafficking [330]. The gene is ubiquitously distributed in adult and fetal human tissues as an approximately 5.4kb transcript [329].However, direct interaction of CD2AP with proteins is involved in cytoskeletal organization [328] which leads to cell–cell interactions [331-332] and endocytosis [333-334]. On the other hand, phosphorylation of tyrosine in response to extracellular stimuli such as growth factors or cell-cell interaction, CD2A subsequently accelerates vesicle formation [329]. In CD2AP, SNPs rs9296559 and rs9349407 are linked with increased LOAD risk [158-159], whereas CD2APrs9349407 is connected with neuritic plaque burden in brains with AD [163]. However, the SNP rs10948363 was most recently recognized through a meta-analysis of 74,046 individuals [160]. Again, the correlation of AD risk variant with greater neuritic plaque burden was reported [163], whereas, a functional screening of AD candidate

genes in drosophila models detected the ortholog of the human CD2AP as a modulator of tau toxicity [335]. As, CD2AP is needed for synapse formation [330], it correlates with Cbl, endophilin, and synaptojanin. On the other hand, CD2AP is involved in mediating vesicular trafficking to the lysosome which is suggested by the observation of the impairment of lysosomal function in cells from CD2AP-deficient mice [333]. Here, ligand binding of CD2AP initiates protein segregation, CD2 clustering, and cytoskeletal polarization [330], as well as the CD2AP mutation in the splice acceptor region of exon 7 was correlated with primary focal segmental glomerulosclerosis [170]. No stable protein has not been recognized from the variant allele for the transcription, it suggests that the disorder may be caused by haplo insufficiency of CD2AP [170].

17. MS4A

The MS4A (membrane spanning four domains, subfamily A) gene cluster is comprised of 16 genes clustered in a 600 kb region of chromosome 11q12 with variable expression in several tissues [336-337]. In addition, it exhibits a suspected role in immune cell functions [337]. Among them, the most important three members named MS4A4A, MS4A4E, and MS4A6E are correlated with AD by GWAS analysis [158,338-339].On the other hand, MS4A genes are distributed in myeloid cells and monocytes encoding proteins with four or more transmembrane domains and also contain cytoplasmic domains at the amino and carboxyl termini, which are typically encoded by distinct exons.The characterization of this gene family is poorly recognized. Structurally and functionally MS4A is as like as CD20 - the high-affinity IgE receptor beta chain [337,340], where CD20 regulates calcium influx after activation of B-cell antigen receptor [341]. The linkage between disequilibrium and genomic structure in the region prevents assignment of the GWAS Signal to a precise gene.Moreover, an MS4A4A mRNA has been found to encode a 205-amino acid protein with a conserved phosphorylation site at the intracellular loop in one observation [336]. Again, in other observation, an MS4A4A mRNA encodes a predicted peptide with 220 amino acids [337].The length of MS4A4E is 220 aminoacids in length where it is 76% identical to MS4A4A for sharing a high degree of homology with the transmembrane and both intracellular domains [337].However, the MS4A4E gene is composed of seven exons that spans more than 23kb [337], whereas MS4A6E is made of four exons to span only 5kb [337].

The SNPs rs983392 (nearMS4A6A) and rs670139 (near MS4A4E) were recognized as AD risk alleles in GWAS in LOAD [158-160], where the SNP rs983392 is related with reduced LOAD risk and rs670139 is are engaged to enhance LOAD risk. The GWAS signal extends MS4A4A and MS4A6A, where recent studies have detected a correlation of the GWAS SNPs with MS4A4A brain expression [205] and MS4A6A blood and brain expressions [342].These observations have confirmed engagement of both genes in AD. MS4A6E mRNA expression and rs670139 are correlated with more advanced tangle and plaque stages in AD brain tissue [161].

Simply, genetics of AD i.e., location, distribution, function, single nucleotide polymorphisms, potential effects on APP and Tau etc. of genes affecting AD are shown in table-1.

Conclusion:

From a genetic slant, Alzheimer's disease is an elusive heterogeneous disorder with both familial and sporadic forms exhibiting tremendous challenge to public health and the health care system with enormous financial burdens. Numerous epidemiologic researches have manifested ample evidences that expanding genomic roadmap of Alzheimer's disease with many genes and with their common and rare variants exhibit a significant role and comprehensive understanding in the development and progression of AD to provide new opportunities and insights into therapeutic targets and strategies. Although whole-genome and whole-exome sequencing studies in large data sets are recognized, the exact genetic influences of this costly and devastating illness are poorly acknowledged with structurally and functionally many unknown genes to understand the mechanisms underlying AD . Potentially, forthcoming observations of AD with approaching studies and analysis of genes and existing evidence of wealth of novel genomic data will provide novel therapeutic approaches to delay and prevent AD from bench to the clinic.

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Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

List of abbreviations

AD, Alzheimer'sdisease; Aβ,amyloidβ; APOE, apolipoproteinE; APP, amyloidprecursor protein; BACE-1,β-secretase beta-site amyloid precursor protein-cleaving enzyme 1; BIN1, bridging integrator 1; CLU, clusterin; CNS, central nervous system; CR1, complement component (3b/4b) receptor 1; CSF, cerebrospinalfluid; GWASs,genome-wide association studies; MAPT, microtubule-associated protein tau; miRNAs,microRNAs; PICALM, phosphatidylinositol binding clathrin assembly protein; pre-MCI, pre-mild cognitive impairment; PSEN1, presenilin1; PSEN2, presenilin2; sAPPα, secretedamyloidprecursor protein-α; SNPs, single nucleotide polymorphism; Cys, Cysteine; Phe, Phenylalanine; Val, Valine; Arg, Arginine.

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Figure 1: Numerous variants of genes involving in Alzheimer's disease risk.

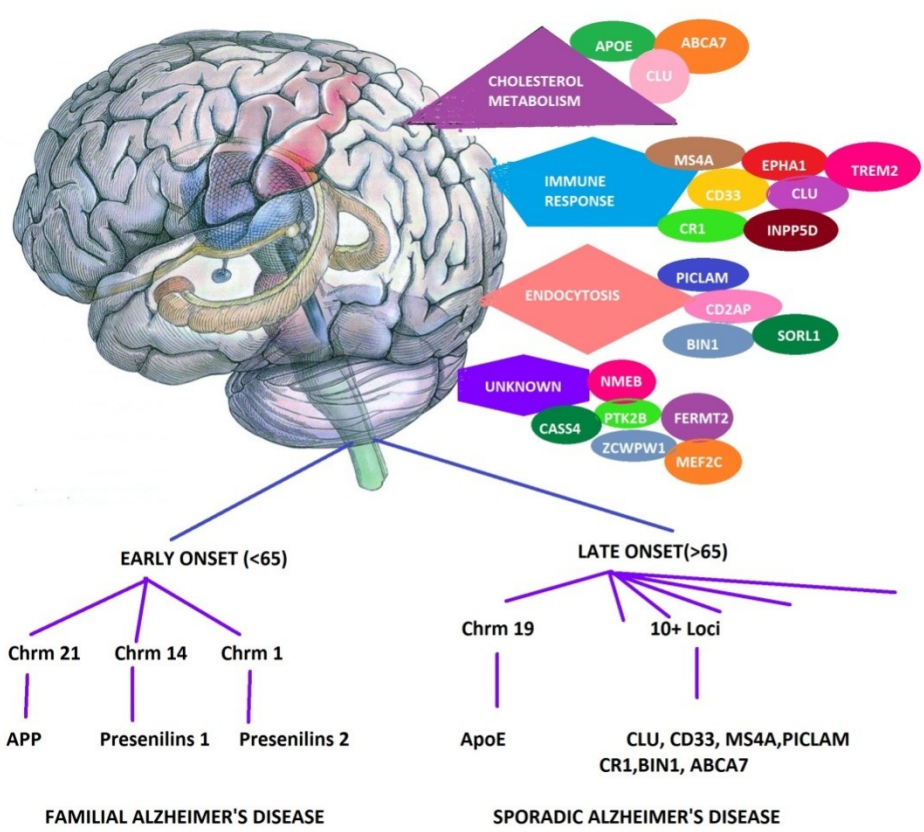

Table 1: Genetic aspects of Alzheimer's disease

Gene	Location	Distribution	Function	Disease SNPs	Potential effects on APP and TAU	Pathways	Reference
APOE	chromosome 19q13.2	Liver, brain, and macrophages. Concentrations of ApoE- in plasma: 40–70mg/ml(approx.) and in cerebrospinal fluid (CSF): 3–5mg/ml (approx.)	Channelize lipids and cholesterols throughout the body, mediates the binding, internalization, and catabolism of lipoproteins in cell, glucose metabolism, lipolytic enzyme activation & several mitochondrial function.	rs429358 and rs7412	Aβ clearance	Lipid metabolism	2, 16,17,20-24,26, 29, 37-38,41
APP	chromosome 21q21	Neurons and Astrocytes	-Invoved in mitochondrial dysfunction and neural plasticity -Acts as a Clinical Immunology and Immunopathology regulator of synapse formation.	Multiple	Cleavage yields Aβ	APP processing	73-76,90-94
PSEN1 and PSEN2	chromosome 14q24.3 and chromosome 1q31-q42	Cell surface, golgi, endoplasmic reticulum, and mitochondria	Constituent of catalytic subunit of gamma-secretase complex; proteolytic cleavage of integral membrane proteins	Multiple	Cleaves APP	APP processing	21,129-130
ABCA7	chromosome 19p13.3	Neuron	Cholesterol metaboliam	rs3764650	Cleaves APP	APP processing	152-155

BIN1	chromosome 2q14.3	Brain and muscle	Endocytosis of synaptic vesicles	rs744373	Moderates tau toxicity	Synapse function	171-175
CLU	chromosome 8p21.1	Whole body,especially brain	Apoptosis, complement regulation, lipid transport, membrane protection, and cell-cell interactions	rs11136000, rs9331888, rs2279590, rs7982, and rs7012010	Aβ clearance	Immune response and lipid metabolism	192-196
EPHA1	chromosome 7q34	Brain and neuron	Brain and neural development; angiogenesis, cell proliferation, and apoptosis	rs11771145	---	Immune response and neural development	210
PICALM	chromosome 11q14.2	Neuron	AP2-dependent clathrin-mediated endocytosis	rs3851179	APP traffickin g and Aβ clearance	Synapse function and endocytosis	21,174, 222-224
SORL1	chromosome 11q23.2	Cell surface to the Golgi-endoplasmic reticulum	Alters endocytosis of the lipids	rs11218343	APP traffickin g	Lipid metabolism, synapse function, and endocytosis	21,237
Tau	chromosome 17	Brain	Stabilization of microtubules, intracellular transport of organelles, secretory vesicles, and other substances such as neurotransmitte rs	Multip le	--------	------	245-246

TREM2	chromosome 6q21.1	Myeloid cells , microglia, monocyte-derived dendritic cells, osteoclasts, and bone-marrow-derived macrophages	Regulates phagocytosis and suppress inflammation reactivity	rs75932628	Aβ clearance	Immune response	270-271
PLD3	chromosome 19q13.2	Neuron	Catalyzing the hydrolysis of phosphatidylcholine	rs145999145	APP trafficking and cleavage	Unknown	285
CD33	chromosome 19q13.3	Myeloid cells and microglia	Moderates sialic acid-dependent binding to cells	rs3865444	Aβ clearance	Immune response	210,297-299
CR1	chromosome 1q32	Phagocytic cells, such as erythrocytes, leukocytes, choroid plexus, microglia, and splenic follicular dendritic cells	Alters cellular binding of immune complexes that activate complement		Aβ clearance	Immune Response	314-316
AKAP9	chromosome 7q21.2	Hippocampus, cerebellum and the cerebral cortex	--------	rs144662445 and rs149979685	----------	--------	91,326
CD2AP	chromosome 6p12	Adult and fetal human tissues	Cytoskeletal reorganization and intracellular trafficking	rs9349407	Mediates tau toxicity	Synapse function and endocytosis	328
MS4A	chromosome 11q12	Myeloid cells and monocytes	Signal transduction	rs610932,rs670139	-------	Immune response	21,336-337