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Genetic underpinnings in Alzheimer's disease – a review

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Abstract: In this review, we discuss the genetic etiologies of Alzheimer's disease (AD). Furthermore, we review genetic links to protein signaling pathways as novel pharmacological targets to treat AD. Moreover, we also discuss the clumps of AD-mediated genes according to their single nucleotide polymorphism mutations. Rigorous data mining approaches justified the significant role of genes in AD prevalence. Pedigree analysis and twin studies suggest that genetic components are part of the etiology, rather than only being risk factors for AD. The first autosomal dominant mutation in the amyloid precursor protein (*APP*) gene was described in 1991. Later, AD was also associated with mutated early-onset (presenilin 1/2, *PSEN1/2* and *APP*) and late-onset (apolipoprotein E, *ApoE*) genes. Genome-wide association and linkage analysis studies with identified multiple genomic areas have implications for the treatment of AD. We conclude this review with future directions and clinical implications of genetic research in AD.

Keywords: AChE; Alzheimer's disease; amyloid-β; APP; BChE; genetics; presenilin; prevalence vs. penetrance of genes.

Introduction: Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia. Age is the strongest risk factor for AD. The projected growth of elderly population (65 years and older) worldwide means that AD cases will increase by 15%–25% by 2050 (Alzheimer's Association, 2014). If no preventive or curative measures are available, this growing number of elderly will pose a huge burden on our societies with

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patients with AD to triple by the mid of the 21st century (Brookmeyer et al., 2007). Indeed, the cost of AD is currently estimated to be $100 billion per year in the United States, $26 and $7 billion of which account for lost productivity of caregivers and for long-term health care, respectively. Therefore, there is an urgent need to develop better diagnostic, management and treatment options for patients to allow delaying or preventing disability, and hence, reduce the financial and emotional costs associated with AD (Bastin and Salmon, 2014).

Current early identification and diagnosis of AD is strongly focused on clinical features such as memory loss, which can be accompanied by a complex array of other cognitive and behavioral symptoms. These clinical features have been related to the onset and spread of underlying amyloid and tau pathology in AD in the brain. Although the substantial advances made over the years have identified that amyloid and tau pathology are the potential cause of AD, the sequence of events that lead to neuronal loss or dysfunction in dementia are still unclear. An understanding of these underlying mechanisms will form the basis for devising better strategies for diagnosis, prevention and treatment (Lippa et al., 2000). Indeed, in particular, genetic risk factors have been little taken into account so far at the clinical level, which have a great potential to reduce risk or even delay the onset of AD. In this article, we review the literature on the underlying genetic underpinnings of AD. We hope that this will inform new clinical approaches to take this information into account.

AD is characterized by the formation of senile plaques and neurofibrillary tangles. The senile plaque core consists primarily of the 4 kDa amyloid-β (Aβ) peptide, which is derived from the amyloid precursor protein (APP) through proteolytic processing by recently identified proteases β and gamma (γ)-secretases. The Aβ peptides of 40 and 42 residues are normally present in the brain, cerebro spinal fluid (CSF) and plasma of normal individuals and are constitutively secreted from cultured cells, suggesting that these peptides do not intrinsically cause AD. However, the levels of Aβ42, the major species of Aβ deposited in the AD brain, are increased by all identified mutations linked to familial AD. Recent studies have shown that in conventional sporadic AD, as in familial AD, there are genetic determinants that result in an increase in levels of Aβ42 in the plasma. Therefore, taking a family history and other genetic factors into account, high plasma Aβ levels may serve as a useful diagnostic marker for predisposition to AD. Evidence suggests that AD is caused by the deposition of Aβ42, which forms toxic aggregates of senile plaques. Thus, the regulation of Aβ42 to lower physiological levels may be an important therapeutic goal for the prevention of amyloidosis in AD. The mechanism by which amyloid deposition eventually leads to neurodegeneration and dementia remains unknown. In fact, its role as the predominant cause of AD has been questioned, as Aβ plaques have been seen in healthy aged individuals with no signs of dementia. Furthermore, the severity of dementia is more closely correlated with numbers of neurofibrillary tangles than with senile plaques. Nevertheless, both observations can be readily explained by assuming that amyloid deposition is an early step in a sequential cascade, which eventually leads to neuronal loss. The genesis of the neurofibrillary tangles may be closely linked to the amyloid-induced neuron loss, either as a direct cause or as a consequence. Understanding the pathways for the induction of neurofibrillary tangles by Aβ may provide useful therapeutic targets and diagnostic markers to cure AD (Hansell et al., 2015).

An overview of the genetic etiology of AD

AD is believed to result from a series of steps in pathogenic pathways leading to amyloid deposition and neurodegeneration in key areas of the brain involved in memory and cognition. Recently, AD has been justified as a genetically complex and heterogeneous disorder. Mutations and polymorphisms in multiple genes (*APP*, *PSEN1*, *PSEN2* and *ApoE*), which are located on at least four different chromosomes (1, 14, 19 and 21), are directly involved in AD (Ridge et al., 2013). Besides *APP*, products of other gene (mainly proteins) are also associated with AD. The *APP*, *PSEN1* and *PSEN2* follow the dominant inheritance pattern and lead to early-onset AD (EOAD) with 100% virtually penetrance, while inheritance of *ApoE* (e4) allele has a strong increasing influence on the development of AD at an earlier age. The early-onset familial AD is also a condition characterized by early-onset dementia (age at onset <65 years) and a positive family history for dementia (Bird, 2008; Wu et al., 2012). There are some recent reports of a susceptibility locus for AD on chromosome 10 and a genetic linkage of AD to its sister chromatid. A linkage of plasma Aβ42 to a quantitative locus on chromosome 10 in the late-onset AD (LOAD) pedigree has also been observed (Shen et al., 2014). Alternative theories about AD, such as considering the AD process as similar to cancer due to a loss of cell cycle control or viewing AD as a result of a dysfunctional signaling pathway mediated by APP, have also been proposed (Bali et al., 2012).

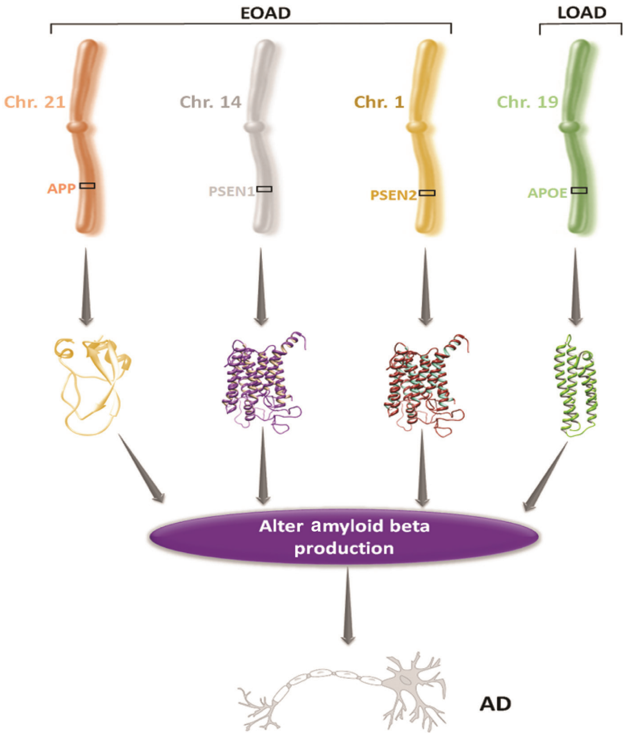

Figure 1: The involvement of some salient genes in the prevalence of AD.
Four different chromosomal location depictions are represented by maroon, purple, yellow and green colors for genes *APP, PSEN1, PSEN2* and *ApoE*, respectively. The gene-mediated proteins are also highlighted in the same colors which govern β peptides in an irregular fashion resulting in AD. Three genes *APP*, *PSEN1* and *PSEN2* are related to EOAD, while *ApoE* is related to LOAD.

Furthermore, other approaches, such as nutritional and environmental factors in AD, are being studied (van de Rest et al., 2015). The depiction of genes and their involvement in AD is illustrated in Figure 1.

AD risk genes and mechanisms of disease pathogenesis

There are some other genes that may cause AD by genetic alterations. Many genetic studies including mutational databases analysis showed that monogenic mutation of a single gene may cause AD by a single nucleotide polymorphism (SNP). Multiple emerging genetic studies have listed various mutations and polymorphisms may contribute to the development of AD. These genes follow the Mendelian pattern of inheritance and serve as risk factors in both EOAD and LOAD (Karch and Goate, 2015). Here, we enlist 31 genes with encoded proteins, which are associated with AD or can modestly increase the AD risk (see Table 1 for details).

Human gene mutations database (http://www.hgmd.cf.ac.uk/ac/index.php) also justified that *APP* possess 35 mutations that are associated with AD. Similarly, *PSEN1, PSEN2* and *ApoE* contain 165, 13 and 13 mutations, respectively. *ADAM10*, *CR1* and *BIN1* are also reported as AD-associated genes.

ADAM10

Wolfsberg et al. (1995) identified several proteins as members of the ADAM family, including ADAM10 and purification of ADAM10 as a TNF-processing enzyme from membrane extracts of a human monocytic cell line (Rosendahl et al., 1997). The *ADAM10* gene is located on chromosome 15 having the total size of 161 172 bases (Yamazaki et al., 1997; Yavari et al., 1998; Prinzen et al., 2005). Functionally, ADAM10 splits ephrin (Eph family receptor), within the ephrin/eph complex and molded between two cell surfaces. After separating ephrin from opposing cells, the ephrin/eph complex is endocytosed. This shedding event in *trans* had not been previously exposed, but may be intricate in other shedding events (Janes et al., 2005; Haass et al., 2012). In neuronal cells, the ADAM10 enzyme is functionally involved in proteolytic activity of the AMPs with α-secretase (Haass et al., 2012). The missense mutational effects in ADAM10 pro-domain are directly linked with LOAD. In Tg2576 AD mice, two rare mutations (Q170H and R181G) impair the pro-domain chaperon functions, decreasing the α-secretase activity, and reducing the adult hippocampal neurogenesis. By knowing such functional effects, presently it has been suggested that ADAM10 could be a novel target for treating AD (Suh et al., 2013). It has also been shown that the ADAM10 gene product in synaptic junctions may interact with AP2 and cause AD (Marcello et al., 2013).

CR1

The *CR1* gene is present on chromosome 1 which encodes the complement receptor type 1 (CR1) protein (Weis et al., 1987). Genetic studies have shown that various mutations of CR1 are associated with the development of AD (Schjeide et al., 2011). Furthermore, AlzGene meta-analysis also shows that *CLU*, *PICALM* and *CR1* SNPs are associated with the development of AD (Corneveaux et al., 2010). A detailed replication study also provides additional evidence that CR1 is related to the risk of developing LOAD

Table 1: Mutations in genes associated with AD.

Genes	Encoded proteins	Locations	Mutations	Penetrance	Prevalence
APP	Amyloid precursor protein	21q21.3	35	High	Low
PSEN1	Presenilin 1	14q24.3	165	High	Low
PSEN2	Presenilin 2	1q31-q42	13	High	Low
ApoE	Apolipoprotein-E	19q13.2	13	Low	High
ADAM10	ADAM domain 10	15q21.3	1	High	Low
CR1	Complement component 3b/4b receptor 1	1q32	8	–	–
BIN1	Bridging integrator 1	2q14	1	–	–
CD2AP	CD2-associated protein	6p12	1	–	–
EPHA1	EPH receptor A1	7q35	1	–	–
CLU	Clusterin	8p21.1	5	Low	High
MS4A6A	Membrane spanning 4-domains A6A	11q12.1	1	–	–
PICALM	Phosphatidylinositol-binding clathrin assembly protein	11q14	1	–	–
ABCA7	ATP-binding cassette subfamily A member 7	19p13.3	1	High	Low
CD33	CD33 molecule	19q13.3	1	–	–
HLA-DRB5	Major histocompatibility complex, Class II, DR Beta 5	6p21.32	8	–	–
PTK2B	Protein tyrosine kinase 2 Beta	8p21.1	1	–	–
SORL1	Sortilin-related receptor, L(DLR Class) A repeats containing	11q23.2-q24.2	6	High	Low
SLC24A4	Solute carrier family 24 member 4	14q32.12	8	–	–
RIN3	Ras and Rab interactor 3	14q32.12	1	–	–
DSG2	Desmoglein 2	18q12.1	1	–	–
INPP5D	Inositol polyphosphate-5-phosphatase D	2q37.1	1	–	–
MEF2C	Myocyte enhancer factor 2C	5q14	17	–	–
NME8	NME/NM23 family member 8	7p14.1	1	–	–
ZCWPW1	Zinc finger CW-type and PWWP domain containing 1	7q22.1	1	–	–
NYAP1	Neuronal tyrosine phosphorylated phosphoinositide-3-kinase adaptor 1	7q22.1	1	–	–
CELF1	CUGBP, Elav-like family member 1	11p11.2	1	–	–
MADD	MAP kinase activating death domain	11p11.2	1	–	–
FERMT2	Fermitin family member 2	14q22.1	1	–	–
CASS4	Cas scaffolding protein family member 4	20q13.31	1	–	–
TREM2	Triggering receptor expressed on myeloid cells 2	6p21.1	7	–	–
PLD3	Phospholipase D family member 3	19q13.2	1	–	–

'–' means that information on the prevalence and penetrance of genes is not known.

(Carrasquillo et al., 2010). The multiple alleles of *CR1* have been observed in association with LOAD (Lambert et al., 2009). The genome-wide association study (GWAS) identified that the variants of CR1 have significant association with AD (Fonseca et al., 2016).

BIN1

Bridging integrator 1 (BIN1), also known as amphiphysin 2, is a novel human gene product with features of a tumor suppressor protein (Negorev et al., 1996). It is encoded by the *BIN1* gene present on chromosome number 2 (Negorev et al., 1996). Various BIN1 isoforms which are expressed in the central nervous system (CNS) may be involved in synaptic vesicle endocytosis. In the CNS, the *BIN1* gene expression can interact with some other regulatory signaling proteins such as synaptojanin, endophilin and clathrin. A mouse model study showed that the *BIN1* gene is critically involved in the cardiac muscle development (Muller et al., 2003). Moreover, mutations in the *BIN1* gene also cause centronuclear myopathy (i.e. the condition which is characterized by muscle weakness) by interfering with remodeling of T tubules and/or endocytic membranes, and that the functional interaction between BIN1 and DNM2 is necessary for normal muscle function and positioning of nuclei (Nicot et al., 2007). The GWAS showed that *BIN1* is significantly associated with AD (Carrasquillo et al., 2011; Hu et al., 2011). The BIN1 protein and its seven isoforms are expressed in the brain and interact with clathrin and AP2/α-adaptin proteins and lead to endocytosis. Epigenetic studies suggested that the *BIN1* gene acts in AD pathogenesis and might be considered as a novel target for AD therapy (Tan et al., 2013). The exact mechanisms of *BIN1* polymorphism and how it leads to AD are still unknown. However, it has been observed that genetic variation in *BIN1* confers AD risk by changing tau pathology (Chapuis et al., 2013).

CD2AP

Mutations in other known genes such as *CD2AP*, *EPHA1*, *MS4A6A/MS4A4E*, *ABCA7* and *CD33* were also found to lead to AD symptoms (Hollingworth et al., 2011). The CD2-associated protein (CD2AP) is a human protein encoded by the *CD2AP* gene located on chromosome 6 (Lowik et al., 2007). Generally, the *CD2AP* gene is involved in the molecular scaffolding which regulates the cytoskeleton of actin protein (Cochran et al., 2015). Furthermore, CD2AP also interacts with filamentous actin and various other membrane-embedded proteins by different actin binding sites. In *CD2AP*, the rs9296559 and rs9349407 SNPs are directly associated with LOAD risk (Hollingworth et al., 2011; Naj et al., 2011). The rs9349407 SNP of *CD2AP* is correlated with neuritic plaque formations in brains of patients with AD (Shulman et al., 2013). A recent meta-analysis of 74 046 individuals showed that the rs10948363 SNP is a risk factor for AD (Lambert et al., 2013). However, the functional impact of this SNP remains unknown since the *CD2AP* gene expression is not changed in AD brains (Karch et al., 2012).

The *CD2AP* knockdown ortholog drosophila model of AD displays tau neurotoxicity (Dustin et al., 1998). The CD2AP mediates functional effects and plays a significant role in the blood-brain barrier integrity and cerebrovascular circulation, which could contribute to its effects on AD risk (Cochran et al., 2015). Polymorphisms in the endocytosis and synaptic function-associated genes (*BIN1, PICALM, CD2AP, EPHA1* and *SORL1*) were identified as LOAD risk factors in several GWAS (Harold et al., 2009; Hollingworth et al., 2011; Naj et al., 2011; Lambert et al., 2013). CD2AP is known as a scaffold adaptor protein (Dustin et al., 1998). It interacts with cortactin, which plays an important role in the regulation of receptor-mediated endocytosis (Lynch et al., 2003). The allelic polymorphism data show that polymorphism of the *CD2AP* gene is a risk factor for AD (Cochran et al., 2015).

EPHA1

Maru et al. (1988) reported the general characterization of the novel receptor tyrosine kinase gene, called *EPH*. EPH receptor A1 (EPHA1) is a protein encoded by the *EPHA1* gene. The *EPHA1* gene is present on chromosome 7q34. The *EPHA1* SNP rs11767557 is related to reduce LOAD risk (Hollingworth et al., 2011; Naj et al., 2011). Recent GWAS data showed that the rs11771145 polymorphism was also associated with reduced LOAD risk (Lambert et al., 2013). However, there is no indication that mRNA expression of *EPHA1* is changed in AD brains (Karch et al., 2012). EPHA1 also plays a significant role in cell and axonal guidance and synaptic plasticity (Martinez et al., 2005; Lai and Ip, 2009). EPHA1 is expressed by CD4-positive T lymphocytes and monocytes (Sakamoto et al., 2011). Moreover, its assessment of genetic variation in this gene revealed that it plays a role in the pathogenesis of AD (Carrasquillo et al., 2011).

MS4A

MS4A is a family of genes such as MS4A4A, MS4A4E and MS4A6E which are poorly characterized. MS4A is structurally similar to CD20 (Howie et al., 2009). FISH and radiation hybrid analysis mapped the *MS4A5* gene to chromosome 11q12-q13 in a cluster with MS4A1, MS4A2 and MS4A3 (Hulett et al., 2001). The *MS4A* genes are expressed in monocytes and myeloid cells. In GWAS, two SNPs including rs983392 (near MS4A6A) and rs670139 (near MS4A4E) were recognized as LOAD risk alleles (Hollingworth et al., 2011; Naj et al., 2011; Lambert et al., 2013). The rs670139 SNP is associated with increased LOAD risk, while rs983392 is correlated with reduced LOAD risk. The SNP variants in MS4A6A were found to be related to AD symptoms. The heterozygous study of patient with AD further supported this association. On inhibition of its expression, it shows neuroprotective effects (Proitsi et al., 2014).

PICALM

Phosphatidylinositol-binding clathrin assembly (PICALM) protein is significantly involved in clathrin assembly, cellular trafficking and regulation of endocytosis. It is tightly associated with iron homeostasis and cell proliferation (Stern et al., 2014). The *PICALM* gene is located on chromosome 11q14 and mostly expressed in neurons (Xiao et al., 2012). Recent studies have demonstrated that rs3851179 and rs541458 of PICALM are directly correlated with reduced LOAD risk (Harold et al., 2009; Lambert et al., 2009, 2013). However, the functional effects of these SNPs still remain unclear. PICALM is also functionally involved in synaptic vesicle fusion to the presynaptic membrane through the trafficking of VAMP2 protein (Harel et al., 2008). A mouse study showed that deficiency of *PICALM* results in abnormal iron metabolism and has no overt neurologic phenotypes (Duce et al., 2010). The *in vitro* analysis showed that the expression of *PICALM* changes the APP trafficking, whereas *in vivo* results depict that overexpression of *PICALM* enhances the plaque deposition in AD transgenic mice (Xiao et al., 2012).

CLU

Clusterin (CLU) is an apolipoprotein encoded by the *CLU* gene located on chromosome 8p21.1 (Dietzsch et al., 1992). The *CLU* gene is organized into nine exons, ranging in size from 47 bp (exon 1) to 412 bp (exon 5), and spanning a region of 16 580 bp (Wong et al., 1994). Generally, CLU is involved in complement regulation, apoptosis, lipid transport, membrane protection and cell-cell interactions (Jones and Jomary, 2002). Various SNPs have been identified in *CLU* that confer protection against LOAD, including rs11136000, rs9331888, rs2279590, rs7982 and rs7012010 (Harold et al., 2009; Hollingworth et al., 2011; Naj et al., 2011). Studies show that the SNPs rs9331888 and rs11136000 are correlated with plasma CLU levels, whereas rs9331888 is also associated with expression of an alternative splice variant (Castellano et al., 2011; Szymanski et al., 2011; Xing et al., 2012). The mRNA of CLU is highly expressed in the brains of patients with AD (Allen et al., 2012; Karch et al., 2012) and can be identified in amyloid plaques (May et al., 1990; Calero et al., 2000). CLU likely influences Aβ clearance, amyloid deposition and neuritic toxicity. Apolipoprotein E (APOE)-deficient and CLU-deficient APP transgenic mice exhibit earlier and more extensive Aβ deposition compared with control mice (DeMattos et al., 2004). CLU is also associated with the complement system. CLU modulates the membrane attack complex, where it inhibits the inflammatory response associated with complement activation (Jones and Jomary, 2002). Because neuroinflammation is a hallmark of AD, SNPs that alter CLU expression or its functions as an amyloid response agent could affect AD pathogenesis and downstream effects. The allelic mutational data show that both genes (*PICALM* and *CLU*) are associated with AD symptoms (Harold et al., 2009).

SORL1

Sortilin-related receptor L (SORL1) protein encoded by the *SORL1* gene is present on 11q23.2 (Jacobsen et al., 2001). SORL1 is a mosaic protein with a domain structure that suggests that it is a member of both the vacuolar protein sorting-10 domain-containing receptor family and the low-density lipoprotein receptor family (Jacobsen et al., 1996). SORL1 is involved in vesicle trafficking from the cell surface to the Golgi-endoplasmic reticulum. *SORL1* is known as an AD risk gene in candidate-based approaches (Rogaeva et al., 2007; Lee et al., 2008). A recent GWAS of 74 046 individuals revealed that the rs11218343 polymorphism near *SORL1* is associated with reduced AD risk (Lambert et al., 2013). It has also been shown that brain DNA methylation in the *HLA-DRB5* and *SORL1* genes is associated with AD pathology (Yu et al., 2015).

ABCA7

ATP-binding cassette transporter A7 (ABCA7) is encoded by the *ABCA7* gene located on chromosome 19p13.3 (Kaminski et al., 2000). ABCA7 protein is a member of ABC transporter superfamily and important for substrate transportation across cell membranes (Kim et al., 2008). The alternative splicing event in ABCA7 generates two transcripts which are expressed in the brain (Ikeda et al., 2003). The *ABCA7* gene confers the risk factor for the development of AD upon allelic variation. Genetic variations in the *ABCA7* gene (c.4416+2T>G and c.5570+5G>C) result in AD susceptibility (Steinberg et al., 2015). There are various SNPs, such as rs3764650, that have been identified as LOAD risk alleles near the *ABCA7* gene by GWAS analysis (Hollingworth et al., 2011; Naj et al., 2011; Lambert et al., 2013). The rs4147929 SNP was highly susceptible in the meta-analysis of 74 046 individuals (Lambert et al., 2013). The impact of these polymorphisms on *ABCA7* gene function and in AD is still poorly understood (Karch et al., 2012; Vasquez et al., 2013). The mRNA expression of ABCA7 in autopsy brain tissue is also correlated with advanced cognitive decline (Karch et al., 2012; Vasquez et al., 2013). *In vitro* analysis showed that Aβ secretion is inhibited by ABCA7 through the stimulation of cholesterol efflux (Chan et al., 2008). Moreover, ABCA7 also modulates the phagocytic activity of apoptotic cells by macrophages (Jehle et al., 2006). It has been observed that ABCA7 may lead to the development of AD by clearing Aβ aggregates or cholesterol transfer to APOE (Chan et al., 2008).

CD33

Sialic acid-binding Ig-like lectin 3 (CD33) is a receptor molecule located on chromosome 19q13.3 (Trask et al., 1993). CD33 is highly expressed on microglia and myeloid cells (Crocker et al., 1997; Griciuc et al., 2013; Malik et al., 2013). The LOAD GWAS analysis showed that CD33 SNPs (e.g. rs3865444) have been found to reduce LOAD risk (Bertram et al., 2008; Hollingworth et al., 2011; Naj et al., 2011). The rs3865444 and rs12459419 SNPs are associated with the increase in CD33 in lacking and modulating the exon 2 (splicing event), respectively (Malik et al., 2013). A recent analysis of data from 74 046 individuals showed that the rs3865444 SNP is failed to attain the genome-wide significance. However, studies suggest that CD33 may play a significant role in AD (Lambert et al., 2013). It has been found that the mRNA expression of CD33 is enhanced in microglia, while the expression in autopsy brain tissue is correlated with advanced cognitive decline (Karch et al., 2012; Griciuc et al., 2013). The inhibition of Aβ phagocytosis effect in immortalized microglial of CD33 is abolished due to a lack of exon 2 (Griciuc et al., 2013). The allelic SNP such as rs3865444 is correlated with reduced CD33 mRNA expression and insoluble Aβ42 in brains with AD (Griciuc et al., 2013). Another significant function of CD33 is Aβ clearance and mediation of neuroinflammatory pathways through microglia in the brain (Griciuc et al., 2013).

PTK2B

Protein tyrosine kinase 2β (PTK2B) which is encoded by the *PTK2B* gene located on 8p21.2 (Herzog et al., 1996) is midway between neuropeptide-activated receptors or neurotransmitters that may enhance Ca^{+2} flux and cascade of mediating signaling like Mitogen-activated protein kinases (Pandey et al., 1999). Another study shows that focal adhesion kinase CAKβ/Pyk2 is directly involved in the long-term potentiation of region CA1 of the hippocampus (Huang et al., 2001). One recent GWAS of 74 046 Caucasian individuals on SNPs (rs10498633) in the *SLC24A4* gene showed that this allele is associated with LOAD risk (Yu et al., 2015). In another GWAS, other genes such as *RIN3*, *DSG2*, *INPP5D* and *MEF2C* were found to play key roles in the development of AD. Furthermore, other reported genes (*NME8*, *ZCWPW1*, *NYAP1*, *CELF1*, *MADD*, *FERMT2* and *CASS4*) are also associated with the risk of developing AD (Karch et al., 2014; Karch and Goate, 2015). Another gene, *TREM2*, also causes the autosomal recessive form of dementia-like symptoms after homozygous mutations (Paloneva et al., 2002). A significant missense mutation (rs75932628-T) in the *TREM2* gene was observed to be associated with AD (Hickman and El Khoury, 2014; Lue et al., 2015). The phospholipase D protein that is encoded by *PLD* is involved in catalyzing the hydrolysis of the phospholipid membrane. Mutations in the *PLD* gene are associated with AD (Wang et al., 2015).

Prevalence and penetrance of genes in AD

Polymorphisms associated with AD appear with various prevalence and penetrance. While variation in some genes is more penetrant (i.e. genes that will definitely lead to develop AD), other variants have low prevalence (i.e. do not commonly occur in AD). Three known genes (*APP, PSEN1* and *PSEN2*) are significantly involved in the prevalence of autosomal dominant AD through fully penetrant mutations (Van Cauwenberghe et al., 2016). Research showed that mutations in the *APP* gene have a 100% penetrance, mostly in carriers (Tanzi, 1999).

The autosomal dominant mutations in *APP* and *PSEN1/2* are recognized as having low prevalence/incidence and high pathobiological impact (early age of onset) (Tanzi, 1999). In detailed analysis, the *PSEN1* mutation causes a severe form of AD with complete penetrance and has a wide variability of onset age (25–65 years), rate of progression and disease severity (Cruts et al., 2012). In contrast, missense mutation carriers in *PSEN2* have incomplete penetrance and mostly affect older age (39–83 years) of onset disease, but the age of onset is highly variable among *PSEN2*-affected families (Sherrington et al., 1995, 1996; Jayadev et al., 2010). The EOAD mutations are related to calamitous phenotypic consequences that present early in the adult life. Therefore, such mutations govern some biological impact and are exceedingly rare. In contrast, the *APOE* E4 polymorphism has a relatively high prevalence, but is weakly penetrant, and carries a low biological impact, as found by the relatively late onset of symptoms (Tanzi, 1999). Genin et al. (2011) reported that *APOE* E4 is consistent with semi-dominant inheritance of a moderately penetrant gene on the basis of Caucasian ancestry using Rochester (USA) incidence data.

Two more genes, such as *SORL1* and *ABCA7*, which are directly involved in AD, have rare variants and seem to have higher penetrance. However, the rare variants of *CLU* have low penetrance (Van Cauwenberghe et al., 2016). Kim et al. (2009) reported that two LOAD-associated mutations in *ADAM10* would appear to be strong candidates for the first rare, highly penetrant pathogenic mutations to be genetically associated with LOAD. Rare highly penetrant mutations in the *ADAM10* gene, Q170H and R181G, were also reported in 7 out of 1000 LOAD families. Both mutations are located in the prodomain region and dramatically impair the ability of ADAM10 to cleave APP at the α-secretase site of APP *in vitro* and *in vivo* (Kim et al., 2009).

In conclusion, while APP and PSEN1/2 are highly penetrant and are associated with AD, *APOE* polymorphism has a high prevalence. Moreover, other rare genetic variants with high penetrance and low prevalence such as *SORL1*, *ADAM10* and *ABCA7* are directly involved in AD pathology. Conversely, other rare variants with low penetrance and high prevalence effects such as *CLU* have also been linked to AD.

Although it is controversial whether mutations in the microtubule-associated protein tau (*MAPT*) gene are associated with AD, they were found to be linked to frontotemporal dementia (Goedert and Spillantini, 2001). Only one mutation in *MAPT* has been associated with AD-like dementia, but it has not been shown to cause AD (Rademakers et al., 2003; Ostojic et al., 2004). One study revealed that mutations in *MAPT* can cause familial frontotemporal dementia (Wilhelmsen et al., 1994), and four other mutations (R406W, V337M, G272V and P301L) have been shown to promote hyperphosphorylation and aggregation of tau protein (Alonso et al., 2004; Iqbal et al., 2010). The aggregates of hyperphosphorylated wild-type *tau* protein have a prevalent pathology of AD and other sporadic tauopathies, and they induce disruption of the microtubules (King et al., 2006). The inhibition of the phosphorylation/aggregation or increased clearance of tau can prevent a molecular cascade that leads to cellular death (Ittner et al., 2010; Piedrahita et al., 2010; Iqbal et al., 2016). Based on its therapeutic functionality, tau protein is considered to be a target of interest in AD (Iqbal et al., 2016). In addition to *APP* and *PSEN1*, there are some studies on other genes which are considered target molecules for AD treatment (Dingwall, 2001). Finally, APP has been proposed to be linked with kinesin-I, a motor protein, and forms a dimeric complex. This possible functional interaction between kinesin-I and APP may implicate the role of alterations in kinesin-I-based transport in the development of AD (Naj et al., 2014).

Many genes along with their risk assessments are still under investigation to confirm their association with AD. However, the largest risk factor for AD is age: cases double with every 5 years between the age of 65 and 85 years. Up to date, there are several risk factors that are known to lead to EOAD. The mutation in *APP* accounts for familial AD. The significance of the *APP* gene is confirmed by the emergence of EOAD in patients with Down's syndrome who have an additional copy of this gene. However, the mechanism by which these genetic alterations influence the Aβ formation remains unclear. Additionally, the E4 allele of *APOE* constitutes a major susceptibility factor for the development of the familial and sporadic forms of LOAD. The prevalence of AD has increased up to 20% among those individuals aged 80 years and older. This may depict that there are some other risk factors that may govern AD symptoms. For example, the transcriptional control of *APP* has not yet been fully explored (Reitz and Mayeux, 2014). Genetic variations in *CLU* (previously known as apolipoprotein J) have been associated with the risk of AD in multiple independent GWAS of diverse ethnic groups. The relationship between CLU levels and the risk for stroke in the current analysis showed that both stroke and dementia share some common factors. It has been observed that CLU was also found to alter the risk of cardiovascular and metabolic diseases which was observed by measuring the CLU (α, β) and C-reactive protein levels (Weinstein et al., 2016).

Research on AD is rapidly expanding and currently encompasses various cellular, molecular, clinical and therapeutic aspects. Reviewing all these diverse areas is beyond the scope of the present work. However, we will briefly address the salient features of the definitive review work of other investigators in different fields of AD. The molecular genetics of AD and its relationship with other primary neurodegenerative diseases have recently been reviewed (Karch et al., 2014). There are also recent studies which explore some protein molecules that are believed to play a role in AD pathogenesis. For example, the cell biology of AD, particularly the roles of secretases (α, β and γ), presenilin 1/2 and notch have been reviewed (Lambert et al., 2013).

Below, we discuss how genes affect the following aspects of AD: (a) memory, (b) amyloid plaques formation and tangle deposition and (c) neurotransmitters related to AD.

Genes and their influence on memory in AD

Progressive memory deterioration is the hallmark feature of AD that results from a number of genetic factors. Because procedural memory is generally preserved in AD (Van Halteren-Van Tilborg et al., 2007), declarative memory is mainly the target of AD studies, which are predominantly focused on the episodic memory subset. Episodic memory is one's collection of interior events and the spatial-temporal-emotional context in which they occurred (Tulving, 1972). Episodic memory is strongly associated with the medial temporal lobe (MTL), in particular the hippocampus and entorhinal cortex (ERC), which are impacted by the progression of AD (Braak and Braak, 1991).

Unsurprisingly, AD-related deficits in episodic memory have widely been found to involve the mediotemporal lobe and related neural networks (Wolk et al., 2011). A relationship between reduced hippocampal volume and episodic memory has been observed by multiple lines of AD research (Mormino et al., 2008; Choo et al., 2010; Sexton et al., 2010). Additionally, studies have found that patients with AD show deterioration of semantic memory, which directly influences episodic memory in the area of recognition and reflects the damage to the hippocampus that occurs early in AD pathogenesis (Drebing et al., 1994).

Genetic factors play a key role in understanding why memory deterioration is characteristic for AD. Expression of the APOE E4 allele is a strong risk factor for AD. Furthermore, patients with AD who are carriers of this allele tend to perform more poorly on episodic memory tasks than non-carriers (Van Der Vlies et al., 2007). A dose-dependent relationship between *APOE E4* and episodic memory task performance has been observed (Kerchner et al., 2014). Moreover, a mouse model with induced expression of *APOE* E4 showed spatial memory deficits and neuronal network dysfunction in the hippocampus, especially in aged mice that were dependent of hippocampal interneurons loss (Andrews-Zwilling et al., 2010; Gillespie et al., 2016). In humans, young *APOE* E4 carriers have a dysfunction in spatial navigation, and disarray of grid-cell-like representations in the ERC with fMRI during a spatial navigation task (Kunz et al., 2015). *APOE E4* may contribute to memory impairment by augmenting *APP* recycling, thereby increasing the production of Aβ peptides. The accretion of Aβ senile plaques and tau-related neurofibrillary tangles have been attributed to cognitive decline in AD; however, there is now substantial evidence that the soluble variants of Aβ and tau are associated with memory loss in AD (see Ashe and Zahs, 2010, for a review).

Rodent studies can give us clearer insight into the relationship between genes and memory, as they are thought to have comparable hippocampus-based memory systems to that of primates (Eriksen and Janus, 2007). These studies have found that periodical injections of synthetic Aβ into normal rats have resulted in transient memory deficits for a sequence lever-pressing task (Cleary et al., 2005). Furthermore, injecting normal rats with Aβ from patients with AD significantly impaired rats' memory of earned behavior in a passive avoidance task (Shankar et al., 2008). Additionally, in a mouse study, it was observed that extracellular accumulation of a 56-kDa soluble Aβ assembly, named Aβ*56, in young mice disrupted memory (Lesné et al., 2006).

It is thought that Aβ activates the phosphorylation of tau proteins (Hernández and Avila, 2010), and it is widely accepted that the accumulation of hyper-phosphorylated tau and resulting neurofibrillary tangles are also implicated in AD memory decline. It has been found that neurofibrillary tangles are not solely responsible for AD memory disturbance (Santacruz et al., 2005). Studies on the toxicity of tau oligomers support this theory. Injecting mutant tau mice with tau oligomer antibodies has shown to improve working memory as well as to maintain the improvement for 2 months (Castillo-Carranza et al., 2014). When pro-aggregants of tau expression are turned off in mice displaying neurological features of AD, their impaired memory is improved (Sydow et al., 2011).

Damage to episodic memory-related brain structures such as the MTL can, at least partly, account for the relationship between aberrant gene expression and memory decline in AD. *APOE E4* has a thinning effect on areas of the brain related to episodic memory including the MTL (Geroldi et al., 1999; Pievani et al., 2009; Wolk and Dickerson, 2010), in particular, the hippocampus (Kerchner et al., 2014). Aβ plaque deposition in humans has a direct link to hippocampal volume which may mediate the relationship between Aβ accumulation and episodic memory (Mormino et al., 2008). Compared to other brain regions, the MTL is the site of a disproportional amount of neurofibrillary tangles (Nestor et al., 2006; Wolk et al., 2011). Tau aggregation and neurofibrillary tangle density in the hippocampus are strong correlates with spatial memory impairment (Mustroph et al., 2012) as well as symptom severity and cognitive decline in AD (Braak and Braak, 1991).

Memory impairment in AD may also be due to disruptions in neural circuitry, such as the progression of neurofibrillary tangle damage to the projection neurons that connect the hippocampus to other parts of the brain. It has been observed that neurofibrillary tangles follow a specific trajectory of accumulation in the ERC similar to the pattern on AD neurodegeneration (Braak and Braak, 1991). Neurofibrillary tangles can affect the hippocampal network by disconnecting the hippocampus from the cerebral cortex (De Calignon et al., 2012). A mouse model for AD (mutated *APP* expression driven only in the ERC) showed a trans-synaptic spread of AD pathology that mimicked the natural history of the disease (Harris et al., 2010; Liu et al., 2012; Khan et al., 2014). Induction of over-expression of mutated human APP and tau in the EC layer II/III spread to specific areas of the hippocampus including the dentate gyrus, CA1 and subiculum (Harris et al., 2010, 2012; De Calignon et al., 2012; Liu et al., 2012; Khan et al., 2014). However, cognitive deficits were only observed in mice having overexpression of mutated human *APP* in the ERC, whereas the overexpression of mutated human tau did not cause cognitive decline in the animals (Harris et al., 2010, 2012). Oligomeric Aβ accumulation and hyper-phosphorylated tau may cause memory deficits by disrupting synaptic plasticity in the hippocampus, such as long-term potentiation (Shankar et al., 2008; Sheng et al., 2012; Tu et al., 2014). Soluble Aβ oligomers have been found to be synapto-toxic (Haass and Selkoe, 2007; Shankar et al., 2008) and may also alter the neural networks involved in learning and memory (Palop and Mucke, 2010).

Genetic influence on amyloid plaque formation and tangle deposition

The most common hypothesis that invokes the implication of APP in the neuronal cell death in AD is the amyloid hypothesis. This hypothesis postulates that deposition of amyloid plaques or partially aggregated soluble Aβ triggers a neurotoxic cascade, thereby causing neurodegeneration and AD. This theory is based on studies suggesting that Aβ is toxic to neurons. The transfected cell line study showed that expressing familial AD mutant genes leads to increased Aβ release. A study showing a close correlation among memory deficits, Aβ elevation and amyloid plaques in transgenic mice supports the amyloid hypothesis (Guerrero et al., 2009).

A modified version of the amyloid hypothesis postulates that the primary contributor to the etiology of AD lies within the cytoplasmic domain of APP. This has also been used to explain the neurotoxicity of the carboxyl-terminal 99-amino-acid fragment of *APP* (*APP-C100*), which includes the 42 residues of Aβ peptide and 57 adjacent amino acids in the carboxyl terminus of *APP*. The mechanism underlying the amyloidogenic and the neurotoxic property of the *APP-100* fragment is still not known (Cerpa et al., 2008).

However, a recent model has been suggested in which intracellular amyloidogenic fragments, such as *APP-C100*, kill neurons 'from inside', in contrast to the popular hypothesis that extracellular Aβ causes neurodegeneration 'from outside'. The *APP-C100* fragment is a normal metabolic product of *APP* in the human brain. Recently, Sykora et al. showed that a 31-residue C-terminal fragment (CTFg) was generated by caspase cleavage of *APP* within its cytoplasmic domain in cells undergoing apoptosis. The expression study justified that the 31-residue fragment was sufficient to induce apoptosis. Deletion of 31 residues from *APP-C100* removed its neurotoxicity, suggesting that this region may mediate toxicity. The proteolysis of *APP* to Aβ40 and Aβ42 should also yield a cognate CTFg of 59 and 57 residues, respectively. All conditions that increase the Aβ42 production automatically increase the CTFg57 fragment. Thus, the observed high correlation between AD and Aβ42 levels may naturally extend to CTFg57 (Sykora et al., 2015).

The second major lesion characteristic of AD is the intracellular deposition of the microtubule-binding protein, tau, in the form of neurofibrillary tangles. Multiple reports suggest that the load of this lesion may be more closely linked to dementia characteristic of AD than amyloid plaque burden. The tau model suggests that the creation of neurofibrillary tangles is the most important characteristic of AD and their density correlates positively with disease severity (Moore et al., 2015). According to the tau hypothesis, structural modification of tau such as hyper-phosphorylation and aggregation interferes with tau function leading to the neuronal dysfunction that may cause AD. In support of this hypothesis, abnormally phosphorylated tau has been observed in the CSF of patients with AD at a very early stage. Furthermore, mutations in *tau* lead to dementia and neurofibrillary tangle formation. However, it is important to note that these mutations do not lead to amyloid deposition characteristic of AD. One report has suggested that the formation of neurofibrillary tangles in P301l tau transgenic mice is induced by Aβ42 fibrils (Götz et al., 2001), and a second report has observed enhanced neurofibrillary degeneration in transgenic mice expressing mutant *tau* and *APP* genes (Lewis et al., 2001). Multiple genes which are associated with Aβ functionality are mentioned in Figure 2.

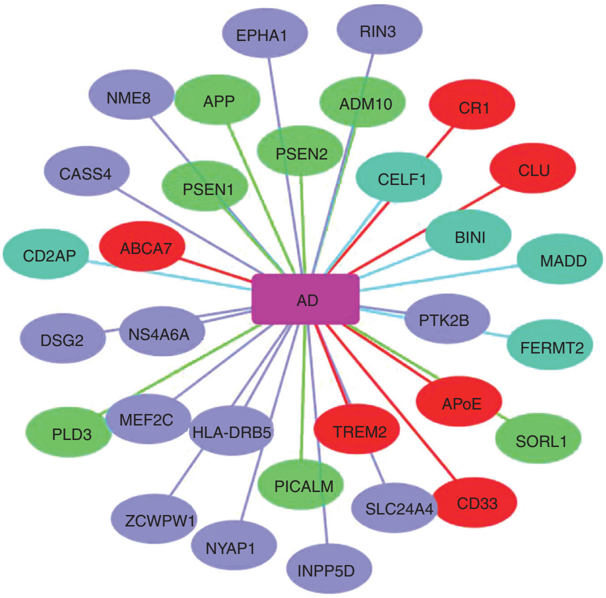

Figure 2: Clump of AD-mediated genes which have functional association with Aβ.
The genes in light green are associated with cleavage of APP. The genes in red are depicted for Aβ. The genes in cyan are associated with tau toxicity and genes in purple are still under investigation.

Genetic and functional deficiencies of neurotransmitters in AD

The relationship between cholinergic neuronal loss and causative amyloid plaques produced from mutant genes is a major area that has been under intensive research. In this regard, several recent studies using cell culture and animal models have shed light onto the effects of anticholinesterase drugs on levels of amyloid proteins. Specific agents possess amyloid-lowering actions as a consequence of their cholinergic as well as non-classical, non-cholinergic activities. This overlap in actions of particular agents may be critical in light of the extensive colocalization of the G1 forms of acetyl- and buteryl-cholinesterase (AChE and BChE) and amyloid plaques, which correlate with plaque load and disease progression. Indeed, there is a colocalization of BChE and all of the pathological hallmarks of AD such as amyloid plaques, neurofibrillary tangles and dystrophic neurons. The reasons underpinning such colocalization have yet to be elucidated, but may be related to a host of non-cholinergic actions associated with AChE and BChE. For example, both enzymes are known to play a role in cell proliferation and differentiation in embryonic brain as well as to bear a structural similarity to adhesion molecules (e.g. neurotactin, neuroligin and gliotactin) that possess trophic and regenerative functions. In addition, BChE has been reported to cleave substrates other than choline esters and likely has amylase and protease activities. Unfortunately, the coexistence of AChE and BChE with Aβ peptide may amplify the toxicity and latterly cause spiraling deleterious events within the brain (Barber et al., 1996). Whether or not cholinesterase agonist can block the interaction between the enzymes and Aβ peptides remains to be elucidated and likely will depend on the wide presence of genetically influenced binding sites involved in the enzyme/drug and enzyme/peptide interactions (Kumar et al., 2015).

In AD, the severe loss of cholinergic neurons in the nucleus basalis and associated areas that form the cholinergic forebrain area, and their projections to the cerebral cortices are marked with decreased levels of acetylcholine and its rate-limiting synthetic enzyme, choline acetyltransferase, in the cortex (Bartus et al., 1982). There is also a matching reduction in the level of the enzyme, AChE, in particular, the G4 form (Atack et al., 1986), which is responsible for terminating the physiological role of acetylcholine at cholinergic synapses. The reduction of cholinergic activity in the central nervous system of patients with AD is controlled by mutant *APP* proteins and correlates with deterioration of scores on dementia rating scales. Coincidental with these changes, the level of its sister enzyme BChE is raised.

BChE shares 65% homology with AChE and likewise metabolizes acetylcholine, but has topological differences. BChE is predominantly localized in the glial cells, increases during AD progression and likely functions to hydrolyze the excessive acetylcholine in the healthy brain. The ratio of AChE to BChE changes from 0.3 in the normal area to 11 in some brain areas as AD develops. Undoubtedly, mismatching results were observed between acetylcholine release and its optimal metabolism that likely contributes to cholinergic dysfunction. In addition, a recent study has demonstrated that 10–15% cholinergic neurons in the hippocampus and amygdala of healthy human brain have BChE, rather than AChE, at the synapse as their metabolizing enzyme (Greig et al., 2000).

Another study hypothesize that specific neuronal pathways may function via BChE, which prompted the recent development of selective reversible agents to inhibit BChE. The selected inhibitors work to augment these pathways and to normalize the BChE to AChE ratio in the AD brain. All these findings, along with the known role of cholinergic neurotransmission in memory processing and storage, led to the hypothesis that cholinergic augmentation might improve cognition in AD. This cognition AD improvement is the result of amplification of acetylcholine's action (muscarinic and nicotinic) through inhibition of its metabolizing enzymes by direct use of agonists that combat the effect of synaptic signaling initiated by *APP* mutant genes (Craig et al., 2011).

Currently, cholinesterase inhibition is the most effective, widely studied and developed approach for treating the symptoms of AD. In this regard, four currently administered drugs for AD (tacrine, donepezil, rivastigmine and galantamine) have been approved by the Food and Drug Administration for prescription as cholinesterase inhibitors. All of them are centrally active and have been shown to improve memory and cognition in some patients with mild-to-moderate AD. Their effects become more apparent after several weeks of therapy and all members of the same drug class vary in some unexpected ways. This dissimilarity likely derives from their divergent chemical structures, different binding sites and pharmacokinetics values of AChE and BChE. Resulting from this, donepezil and galantamine possess selectivity for the acetyl form of cholinesterase, whereas both tacrine and rivastigmine co-inhibit both AChE and BChE. Furthermore, likely due to their mechanisms of binding action and long half-lives, the former two agents gradually induce up-regulation of their target AChE, whereas the latter do not. The other differences plausibly account for the observation that patients not benefiting from one agent may benefit from another, although all are of the same class (Zemek et al., 2014).

Conclusions and future directions

Genes are now considered key players to explore the etiology of AD. In this article, we reviewed some known genetic risk and protective factors of AD. We discussed 31 genes with respect to their mutations and known functional effects (penetration/prevalence). The recognition of AD risk variants may provide a new gateway to properly understand the underlying AD mechanism. Recently, the novel identified genes showed significance association with Aβ production and clearance, which exposed significance of this mechanistic pathway (Aβ) in the pathogenesis of AD. In our review, we highlighted the few genes such as *ABCA7, BIN1, CASS4, CD33, CD2AP, CELF1, CLU, CR1, DSG2, EPHA1, FERMT2, HLA-DRB5-DBR1, INPP5D, MS4A, MEF2C*, *NME8, PICALM, PTK2B, SLC24H4-RIN3, SORL1* and *ZCWPW1* that are associated with AD risk.

Mutated genes and common variants actively participate in the pathogenesis of AD by exploring the underlying Aβ-signaling pathways. Most of the genes (*APP, PSEN1, PSEN2* and *APOE*) were understood as key regulators in the Aβ production and have a significant effect on the synaptic receptors in both EOAD and LOAD stages. Multiple cellular and molecular genetic approaches showed the significance of these genes-mediated proteins and their downstream signaling pathways which may be considered as novel targets in the therapeutics of AD. Recently, different research groups have synthesized their agonists by taking these proteins as novel targets to treat AD. Multiple factors such as nutritional, genetic and environmental stress may also highlight more effective and preventive approaches for AD. Taken together, this review gives a brief update of genetic etiology of AD and of the mechanistic pathways of common mediated proteins which may be considered as novel targets against AD pathology in future. Studies on neurobiological mechanisms to provide new targets for drug development in AD are expanding rapidly, and current investigations cover a broad area of cellular, molecular, genetic and clinical research.

Herein, we have made an attempt to review recent trends in AD research in these aforementioned areas. The molecular genetics of AD and the role of key proteins (known and to be discovered) that are believed to participate in AD pathogenesis are important fields for further research. Similarly, the cell biology of AD, particularly the roles of secretases, presenilin, notch and tau proteins, should provide new light on the cascade of AD neurodegenerative pathways. In addition to *APP* and *PSEN1*, there is significant active research underway in the development of new inhibitors for *PSEN1* and γ-secretase as targets for the treatment of AD. Research is also underway to dissect and characterize *APP* genetic regulatory elements for the development of potential drug targets. Furthermore, research on the *CLU*, *ABAC7* and *SORL1* genes could produce novel therapeutic targets for the treatment of AD. Newer technologies, such as DNA microarray technologies to study gene expression profiles in AD, proteomics to analyze the protein profiling of AD brain tissues and transgenic mouse models of AD, should yield new and useful clues to further characterize the pathobiochemical processes of AD. Other approaches, such as nutritional, genetic and environmental factors, may also highlight more effective preventive strategies for AD. Indeed, our current understanding of the role of oxidative stress in AD has resulted in the wide use of antioxidants, such as vitamin E, to potentially delay the progression of AD. Finally, it should be stressed that both early diagnosis of AD and the development of quantitative markers to better follow the course of the disease are also extremely important for the evaluation and successful development of therapeutic strategies (Imtiaz et al., 2014).

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