# Genetic Markers of Alzheimer's Disease

Matea Nikolac Perkovic and Nela Pivac

**Abstract**

Alzheimer's disease is a complex and heterogeneous, severe neurodegenerative disorder and the predominant form of dementia, characterized by cognitive disturbances, behavioral and psychotic symptoms, progressive cognitive decline, disorientation, behavioral changes, and death. Genetic background of Alzheimer's disease differs between early-onset familial Alzheimer's disease, other cases of early-onset Alzheimer's disease, and late-onset Alzheimer's disease. Rare cases of early-onset familial Alzheimer's diseases are caused by high-penetrant mutations in genes coding for amyloid precursor protein, presenilin 1, and presenilin 2. Late-onset Alzheimer's disease is multifactorial and associated with many different genetic risk loci (>20), with the apolipoprotein E ε4 allele being a major genetic risk factor for late-onset Alzheimer's disease. Genetic and genomic studies offer insight into many additional genetic risk loci involved in the genetically complex nature of late-onset Alzheimer's disease. This review highlights the contributions of individual loci to the pathogenesis of Alzheimer's disease and suggests that their exact contribution is still not clear. Therefore, the use of genetic markers of Alzheimer's disease, for monitoring development, time course, treatment response, and prognosis of Alzheimer's disease, is still far away from the clinical application, because the contribution of genetic variations to the relative risk of developing Alzheimer's disease is limited. In the light of prediction and prevention of Alzheimer's disease, a novel approach could be found

M. Nikolac Perkovic · N. Pivac (✉)
Division of Molecular Medicine, Rudjer Boskovic Institute,
Bijenicka 54, Zagreb 10000, Croatia
e-mail: npivac@irb.hr



Y.-K. Kim (ed.), *Frontiers in Psychiatry*, Advances in Experimental Medicine and Biology 1192, https://doi.org/10.1007/978-981-32-9721-0_3

in the form of additive genetic risk scores, which combine additive effects of numerous susceptibility loci.

**Keywords**
Alzheimer's disease · Genetics · GWAS · Late-onset · Markers

## Introduction

### Alzheimer's Disease

Alzheimer's disease is a complex and heterogeneous brain disorder that can be classified, according to its stages, into dementia in Alzheimer's disease (F.00) and Alzheimer's disease (G.30), according to ICD-10. Namely, it is a severe neurodegenerative disease and the predominant form of dementia (50–75%), but when behavioral and psychotic symptoms of dementia (BPSD) develop during the course of Alzheimer's disease, it has to be treated as a severe mental, i.e., psychiatric disorder. These neuropsychiatric symptoms include depression, apathy, anxiety, irritability, agitation, euphoria, hallucinations, disinhibition, aberrant motor behavior, elation, delusions, and sleep or appetite changes; and they can occur in the early as well as in the middle and late stages of Alzheimer's disease [1].

The first sign of dementia in Alzheimer's disease is the gradual worsening of the ability to remember new information. However, during the course of Alzheimer's disease, multiple cognitive domains are disrupted [2, 3]. The cognitive disturbances affect universal domains such as attention, working memory, executive function, procedural learning and memory, speed of processing, fear-extinction learning and semantic memory, and some higher domains that include episodic memory, social cognition, theory of mind, verbal learning, memory, and language (i.e., use and understanding) [3, 4]. Alzheimer's disease is a slow, irreversible, progressive, complex, and lethal disorder, which represents a major health problem and fatal global epidemic worldwide [3]. It is characterized by progressive cognitive decline, disorientation, behavioral changes, and death. A latency phase of the Alzheimer's disease is without clinical symptoms although the pathophysiological processes are active [2]. The clear etiology of Alzheimer's disease is still unknown. However, the main risk factors are older age, genetic predisposition (especially the apolipoprotein E (ApoE) ε4 genotype), gender (female predominance), and presence of the mild cognitive impairment, but there are also modifiable factors such as cardiovascular risk factors, hypertension, diabetes, obesity, smoking, and high cholesterol levels [3]. Insulin signaling dysfunction and brain glucose metabolism disturbances are hallmarks of Alzheimer's disease, and therefore recently Alzheimer's disease was suggested to be considered as type 3 diabetes [5].

## Genetic Background of Alzheimer's Disease

Alzheimer's disease can be divided into autosomal dominant Alzheimer's disease (or early-onset familial Alzheimer's disease), other cases of early-onset

Alzheimer's disease, and late-onset Alzheimer's disease [6]. Genetic background of Alzheimer's disease differs between early-onset familial AD, other cases of early-onset Alzheimer's disease, and late-onset Alzheimer's disease. Early-onset familial Alzheimer's disease, with a prevalence less than 1%, is caused by high-penetrant mutations in genes coding for amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Late-onset Alzheimer's disease is multifactorial and associated with many different genetic risk loci (>20), with the ApoE ε4 allele being a major genetic risk factor for late-onset Alzheimer's disease. Genome-wide association studies (GWAS) offered insight into many additional genetic risk loci involved in the genetically complex nature of late-onset Alzheimer's disease. This review focuses on the recent data from comprehensive meta-analysis and GWAS. However, it should be highlighted that the exact contributions of individual loci to the pathogenesis of Alzheimer's disease still remain unclear to date.

## Early-Onset Familial Alzheimer's Disease

The discovery of the association between mutations in *APP*, presenilin *PSEN1* and *PSEN2* genes and the development of early-onset familial Alzheimer's disease provided knowledge about the molecular mechanisms underlying the Alzheimer's disease pathogenesis.

### Amyloid Precursor Protein

The enzymatic cleavage of APP can lead to the formation of amyloid β-peptide (Aβ), which can be 38 to 43 amino acids long. Cleavage of APP by α- and γ-secretases results in the generation of nonpathogenic peptides, secreted form of APP (sAPPα) and C-terminal fragments. This pathway is known as nonamyloidogenic or constitutive pathway. Amyloidogenic pathway involves the proteolysis of APP by β- and γ-secretase, resulting in the formation of sAPPα, C-terminal fragments, and Aβ. We differentiate two main forms of Aβ, Aβ1–40, and Aβ1–42. Amyloid plaques are most commonly formed from more amyloidogenic Aβ1–42 form.

According to Alzheimer Disease and Frontotemporal Dementia Mutation Database (http://www.molgen.ua.ac.be/ADmutations/) and Alzforum (https://www.alzforum.org/mutations/app), there are around 35 different *APP* mutations that have been associated with Alzheimer's disease pathogenesis. These mutations include *APP* gene locus duplications and different point mutations in coding region of *APP* gene, resulting in an amino acid substitution. Duplication of the whole gene/locus lead to elevated levels of APP and Aβ, and increase the ratio of Aβ1–42 to Aβ1–40. Missense mutations can have different effects, depending on their position. If these mutations cause amino acid substitution near the β-proteolytic cleavage site (N-terminal of Aβ), they usually lead to increased β-secretase cleavage, increased total Aβ production, and increased aggregation and fibril formation (Table 1). Missense mutations in the Aβ sequence in general increase Aβ aggregation and fibril formation (Table 1). If the missense mutation is

near the C-terminal of Aβ, then it will increase the relative production of Aβ1–42, compared to Aβ1–40 (Table 1).

### Presenilin 1 and Presenilin 2

PSEN1 and PSEN2 are two homologous multi-transmembrane proteins that share around 67% of the sequence [7], and they represent the catalytic core of γ-secretase complex. These proteins are also involved in the cleavage of some other proteins, like cadherins, low-density lipoprotein receptor (LDLR)-related proteins, Notch-1 and ErbB4 [8–11]. At the cell level, presenilins can be found in the nuclear membrane, endoplasmic reticulum, the trans-Golgi network and at the plasma membrane. They are also widely expressed throughout the organism.

Mutations in *PSEN1* and *PSEN2* genes are the most frequent known cause of early-onset familial Alzheimer's disease, with emphasis on *PSEN1* gene. Mutations in these two genes usually cause an impairment in γ-secretase activity and lead to an increase in the ratio between Aβ1–42 and Aβ1–40, as a consequence of Aβ1–42 overproduction or Aβ1–40 underproduction, or as a combination of both (Table 1). *PSEN1* mutations were associated with the earliest disease onset ages, with an average age of onset around 43 years, from 25 until 65 years of age [12]. In *APP* mutation carriers the disease starts on average 8.4 years earlier (age of onset between 35 and 65 years of age), and in *PSEN2* mutation carriers on average 14.2 years earlier, with a much older age of onset (between 45 and 70 years of age) [12].

## Late-Onset Alzheimer's Disease

Most of the genes that have been associated with late-onset Alzheimer's disease, detected through different candidate genes studies and GWAS, are involved in cholesterol and lipid metabolism (genes coding for ApoE (*APOE*), sortilin-related receptor-1 (*SORL1*), ATP-binding cassette subfamily A member 7 (*ABCA7*), and clusterin (*CLU*)), immune system and inflammation (genes coding for complement C3b/C4b receptor 1 (*CR1*), CD33 antigen, membrane-spanning 4-domains, subfamily A member (*MS4A*), triggering receptor expressed on myeloid cells 2 (*TREM2*), member of the major histocompatibility complex class II HLA-DRB5/HLA-DRB1, and a SH2-containing inositol 5-phosphatase 1 (*INPP5D*)), and/or endosome cycling (genes coding for bridging integrator protein-1 (*BIN1*), CD2-associated protein (*CD2AP*), phosphatidylinositol binding clathrin assembly protein (*PICALM*), ephrin type-A receptor 1 (*EPHA1*)). However, there are also studies that implicate some other genes, whose function is not so well known and described, with Alzheimer's disease pathology, like genes coding for thioredoxin domain-containing protein 3 (*NME8*), CUGBP Elav-like family member 1 (*CELF1*), cas scaffolding protein family member 4 (*CASS4*), protein-tyrosine kinase 2-beta (*PTK2B*), zinc finger CW-type PWWP domain protein 1 (*ZCWPW1*), fermitin family homolog 2 (*FERMT2*), sodium/potassium/calcium exchanger 4 (*SLC24A4*), and Ras and Rab interactor 3 (*RIN3*) [13–19]. In this

**Table 1** Genes, chromosomes, pathways, and polymorphisms associated with Alzheimer's disease

| Gene | Chr | Pathway | Mutations/Polymorphisms | | References |
|---|---|---|---|---|---|
| | | | ID | Potential effect | |
| APP | 21q21 | APP processing | dupAPP[ALZ254], dupAPP[EXT187], dupAPP [3], dupAPP[EXT144], dupAPP[EXT145], dupAPP [2], dupAPP [1], dupAPP[PED3281], dupAPP[VI], dupAPP[EXT054], dupAPP[EXT279], dupAPP [4], dupAPP[EXT298], dupAPP[Swedish], dupAPP [5], dupAPP[PED2945], dupAPP[BRB] | Increased production of Aβ | [57–61] |
| | | | rs63751263, rs63750445, rs63750064, Glu682Lys, rs63751039, ΔGlu693 | N-terminal of Aβ peptide (β-secretase site, increased total Aβ production) | [62–69] |
| | | | rs63750973, rs63750734, rs63750868, rs63750399, Ile716Phe, Ile716Thr, Ile716Met, rs63750264, rs63750264, rs63750264, rs63751122 | Mutations in Aβ sequence (increased aggregation and fibril formation) | [57, 61, 70–114] |
| | | | rs63750151 | C-terminal of Aβ peptide(γ-secretase site, increased Aβ1-42 production) | [115] |
| PSEN1 | 14q24.3 | APP processing | rs63749824, rs63749967, rs63751141, rs63750831, rs63750601, rs63750852, Thr99Ala, rs63750325, Phe105Val, Phe105Cys, rs63750321, Arg108Gln, rs63749962, rs63750450, rs63750730, rs63750730, rs63750550, rs63749805, rs63750800, Glu120Gly, rs63751272, rs63750378, His131Arg, Leu134Arg, rs63750353, rs41345849, rs63751106, rs63750522, Met139Ile, Ile143Val, rs63750322, rs63750004, rs63751071, rs63750306, rs63750306, rs63750391, rs63750907, Leu150Pro, rs63751441, rs63751292, Tyr159Phe, rs63749885, His163Pro, rs63751010, Leu166Val, rs63751458, rs63750265, Ile168Thr, rs63750963, Leu173Phe, rs63751144, rs63751025, rs63749911, rs63749806, rs63750155, rs63750311, Ile202Phe, rs63750569, rs63750082, rs63749880, rs63750053, Ser212Tyr, rs63750861, rs63750861, rs63751309, His214Asp, rs63751003, Gly217Arg, rs63749987, rs63750761, Leu219Arg, rs63750009, rs63751072, rs63749961, rs63749970, Ser230Ile, Ser230Arg, rs63749836, rs63750799, rs63751287, rs63751024, rs63751479, rs63751130, Leu235Arg, rs63750858, Ile238Met, rs63750888, rs63750526, Leu248Pro, Leu248Arg, rs63751163, rs63751320, rs63751420, rs63750248, rs63750543, rs63751102, rs63751229, rs63750779, rs63750886, rs63750772, Glu273Gly, rs63750284, Ala275Val, rs63750231, Leu282Phe, rs63750050, rs63751139, rs63751235, Arg352Cys, rs63751164, rs63751174, Ser365Ala, rs63750941, rs63751051, rs63750323, rs63750646, rs63749860, Phe386Leu, rs63750883, rs63751066, rs63751416, rs63750929, Ala396Thr, rs63751254, Ile408Thr, rs63750227, rs661, rs63751316, rs63750802, rs63751032, rs63751223, rs63750083, rs63750528, rs63750341, rs63750001, rs63749925, rs63750249, Ile439Ser | Increased ratio of Aβ42 to Aβ40 | [61, 75, 76, 82, 87, 94–96, 104–106, 110, 114, 116–224] |
| | | | Intron4 (InsTAC), rs63750879, Ser169del, Leu174del | Increased ratio of Aβ42 to Aβ40 | [94–96, 106, 205, 225–227] |

(continued)

**Table 1** (continued)

| Gene | Chr | Pathway | Mutations/Polymorphisms | | References |
|---|---|---|---|---|---|
| | | | ID | Potential effect | |
| PSEN2 | 1q31–q42 | APP processing | Gly34Ser, rs150400387, Pro69Ala, Arg71Trp, rs63749851, Glu126Lys, rs63750197, Val139Met, Asn141Tyr, rs63750215, Ile235Phe, rs200670135, Leu238Pro, rs63749884, Ala258Val, Pro348Leu, Val393Met, Thr421Met, rs63750666, rs63750110, rs63750812, Lys161Arg, Ser175Cys, Val214Leu, rs63750880 | Increased ratio of Aβ42 to Aβ40 | [7, 61, 62, 71, 82, 86, 87, 106, 107, 110, 114, 144, 184, 186, 188, 189, 204, 211, 220, 228–244] |
| APOE | 19q13.2 | Lipid metabolism | rs429358+rs7412 | Less efficient clearance of soluble Aβ, amyloid plaques and/or neurofibrillary tangles (ApoE4) | [56, 245–251] |
| SORL1 | 11q23/24 | Endocytosis Lipid metabolism | rs12285364, rs668387, rs3781835, rs117260922, rs143571823, rs11218343, rs2298813 | Mutations possibly leading to SORL1 underexpression and overexpression of Aβ | [14, 34, 35, 252] |
| ABCA7 | 9p13.3 | Lipid metabolism Immune response | rs3752246, rs3764650, rs115550680 | Altered lipid homeostasis and/or immune response and/or the clearance of amyloid plaques | [37, 39, 47, 253] |
| CLU | 8p21–p12 | Cholesterol metabolism and immune response | rs11136000, rs1532278, rs9331888, rs867230, rs9331908, rs7982, p.T445_D447del | Alterations in CLU expressions and subcellular localization, modulating amyloid deposition | [29–32, 151, 254] |
| CR1 | 1q32 | Immune response | rs3818361, rs6656401, rs6701713, rs1408077, LCR1-CNV | Alter the binding activity of CR1 and affect the CR1-mediated clearance of Aβ from blood | [14, 30, 37, 45, 46, 255] |
| CD33 | 19q13.3 | Immune response | rs3865444, rs3826656, rs12459419 | Possible effect on splicing efficiency or CR1 expression affecting Aβ clearance and microglia-mediated neuroinflammatory pathways | [37, 256, 257] |

(continued)

**Table 1** (continued)

| Gene | Chr | Pathway | Mutations/Polymorphisms | | References |
|---|---|---|---|---|---|
| | | | ID | Potential effect | |
| MS4A family | 11q12.2 | Immune response | rs610932, rs670139, rs4938933, rs667897 | Alterations in MS4A expression affect Aβ generation, tau phosphorylation, and apoptosis by regulation of calcium homeostasis | [37, 47, 53, 258] |
| TREM2 | 6p21.1 | Immune response | rs75932628, rs6916710, rs6922617 | Decreased affinity of TREM2 for its ligands could affect the clearance of Aβ or lead to systemic inflammatory response | [92, 259–261] |
| BIN1 | 2q14.3 | Endocytosis Synapse function | rs744373, rs7561528 | Increased BIN1 expression modulates Tau pathology | [29, 30, 40, 41] |
| PICALM | 11q14 | Endocytosis Synapse function | rs561655a, rs3851179, rs541458 | Increased PICALM expression facilitates Aβ and tau clearance | [14, 29, 42, 262, 263] |
| CD2AP | 6p12 | Endocytosis Synapse function | rs9296559, rs9349407 | Reduced CD2AP expression associated with increased neuritic plaque pathology | [37, 47, 55, 264] |
| EPHA1 | 7q34 | Immune response | rs11771145, rs11767557 | Regulate EPHA1 gene expression and interferes with the pathological alteration in AD | [37, 47, 265] |

chapter, some of the most interesting genes found to be associated with late-onset Alzheimer's disease will be described, with their possible involvement in certain biological pathways and mechanisms that might be relevant for Alzheimer's disease pathology.

### Apolipoprotein E

One of the major risk loci for late-onset Alzheimer's disease is the ε4 allele of *APOE* gene, gene coding for the main apolipoprotein in the central nervous system. This glycoprotein plays an important role in lipid transport, and it has an undeniable role in growth, repair, reorganization, and maintenance of neurons. ApoE facilitates the cellular uptake of lipoproteins by binding to the members of LDLR family, or it takes part in the activation of signaling pathways involved in modulating lipid homeostasis [20]. Two amino acid substitutions at the positions 112 and 158 lead to three possible ApoE isoforms, ApoE2, ApoE3, ApoE4, which are encoded by three common alleles (ε2, ε3, ε4). The ε4 allele has been associated with Alzheimer's disease, and it is considered as a most important risk factor in the case of late-onset Alzheimer's disease (Table 1). The carriers of *APOE* ε4 allele have an earlier age of onset of Alzheimer's disease, and they also tend to have more pronounced accumulation of neurofibrillary tangles and amyloid plaques [21]. However, *APOE* ε2 allele was associated with reduced risk of developing Alzheimer's disease, with reduced accumulation of neurofibrillary tangles and amyloid plaques [22, 23], but also with significantly larger regional cortical thicknesses and volumes in subjects with cognitive impairment or Alzheimer's disease [24]. The amino acid substitution at the position 158 (arginine to cysteine) impairs the binding of ApoE2 to LDLR and its ability to promote clearance of TG-rich lipoprotein remnant particles. ApoE4 is characterized by an amino acid substitution at the position 112 (cysteine to arginine) that affects the stability of the N-terminal domain helix bundle and C-terminal domain, resulting in enhanced lipid-binding ability of ApoE4 [20] and less efficient clearance of soluble Aβ, amyloid plaques and/or neurofibrillary tangles [25].

### Clusterin

Clusterin is a highly glycosylated cell-aggregating factor that is involved in different processes, including complement inhibition, inflammation, apoptosis, and lipid transport [26]. As a chaperone, it could be involved in the amyloid aggregation and pathogenesis of Alzheimer's disease [27]. Evidence suggests that clusterin forms complexes with Aβ in cerebrospinal fluid that are able to cross the brain–blood barrier [28]. Few GWAS studies suggested clusterin as a potential biomarker of Alzheimer's disease [29, 30]. A single nucleotide polymorphism (SNP) in the *CLU* gene was suggested to be associated with Alzheimer's disease pathology by affecting alternative splicing of *CLU* [31]. Other rare non-synonymous single nucleotide variations have also been identified, along with an in-frame 9-bp deletion, that could possibly/probably disturb clusterin structure and function

(Table 1). Findings summarized in Table 1 include mutations that could affect the β-chain domain of clusterin or are positioned in the intron sequence with high regulatory potential [32].

### Sortilin-Related Receptor-1

Sortilin-related receptor-1 (SORL1) is considered a member of low-density lipoprotein receptor family and a member of the vacuolar protein sorting 10 (Vps10) family of receptors. There are indications that SORL1 could be involved in APP processing and trafficking, and that it could be responsible for directing Aβ toward lysosomes [33]. However, as a member of LDLR family and an ApoE receptor, SORL1 also plays a role in lipid metabolism. SORL1 was first suggested as a potential risk factor for late-onset Alzheimer's disease by Rogaeva and colleagues [34], and this was later confirmed by other more comprehensive studies [14, 35]. One of the possibilities is that the mutations in *SORL1* gene (Table 1) affect *SORL1* expression and BDNF-induced APP processing [36].

### ATP-Binding Cassette Subfamily A Member 7

ATP-binding cassette subfamily A member 7 (ABCA7) belongs to a family of ABC transporters that are responsible for transporting various molecules across cellular membranes. The exact function of ABCA7 still unknown, but there are indications that this protein could play a role in lipid homeostasis and the immune system. Therefore, the mutations in *ABCA7* gene could contribute to Alzheimer's disease development by affecting its interaction with ApoE and lipid metabolism and/or by modulating the immune response and the clearance of amyloid plaques. ABCA7 was associated with Alzheimer's disease in 2011 in a large-scale GWAS analysis [37]. The reported mutations in *ABCA7* gene (Table 1) mostly lead to alterations in gene expression [38], but some rare loss-of-function mutations have also been reported [39].

### Bridging Integrator Protein-1

Bridging integrator protein-1 (BIN1) is an amphiphysin involved in caspase-independent cell death pathways and clathrin-mediated endocytic pathway [29, 30]. Few GWAS have identified mutations in *BIN1* gene (Table 1) associated with Alzheimer's disease diagnosis [29, 30, 40]. The study by Chapuis and colleagues [41] suggested that increased *BIN1* gene expression in dementia patients mediates Alzheimer's disease risk by modulating tau pathology.

### Phosphatidylinositol Binding Clathrin Assembly Protein

Phosphatidylinositol binding clathrin assembly protein (PICALM) is, similarly to BIN1, involved in clathrin-mediated endocytic pathway. Certain SNPs in *PICALM* gene (Table 1) were found to be associated with the risk of developing Alzheimer's disease. There are even indications that this protein is involved in the internalization of APP and Aβ production [42], Aβ and tau clearance [43, 44].

### Complement C3b/C4b Receptor 1

Complement C3b/C4b receptor 1 (CR1) is a glycoprotein belonging to the receptors of complement activation (RCA) family. CR1 regulates complement activation, but it is also participating in innate immune responses. It is expressed by many cell types, including erythrocytes, leukocytes, and dendritic cells. Different SNPs and an intragenic functional copy-number variation [45, 46] in *CR1* gene (Table 1) have been associated with increased risk of developing Alzheimer's disease. Mentioned copy-number variation in *CR1* gene results in two different CR1 protein isoforms (CR1-F and CR1-S), differentiating in the number of C3b/C4b, and cofactor activity binding sites [45, 46], but the exact mechanism of the association with Alzheimer's disease pathology is not known.

### CD33

CD33 is a cell surface receptor that mediates cell–cell interaction. This member of the sialic acid-binding receptor family transmembrane proteins is an important mediator of cell growth and survival, and one of key players in clathrin-independent endocytic pathway and innate and adaptive immune system functions [37, 47]. There is evidence of a positive correlation between the expression of CD33 in microglial cells, amyloid plaque burden and decline in cognitive functions [48, 49]. Different GWAS found a significant association between certain SNPs (Table 1) and late-onset Alzheimer's disease. One of these SNPs, rs3865444, was associated with the modifications in CD33 level and amyloid pathology [49, 50].

### Membrane-Spanning 4-Domains Subfamily A Gene Cluster

Membrane-spanning 4-domains subfamily A gene cluster (MS4A*)* gene products are transmembrane proteins with at least four transmembrane domains. The genes belonging to this cluster family are not very well characterized, but they might play a role in immunity and intracellular protein trafficking in microglia [51, 52]. There are indications that genes within the *MS4A* gene cluster regulate soluble triggering receptor expressed on myeloid cells 2 (sTREM2) levels, linking this gene cluster family with Alzheimer's disease pathogenesis [52]. Three members of MS4A family (MS4A4A, MS4A4E, MS4A6E) have been linked to Alzheimer's disease by GWAS (Table 1), more precisely, SNPs rs670139 (*MS4A4E*), rs4938933 and rs1562990 (region between *MS4A4E* and *MS4A4A*), and rs610932 and rs983392 (*MS4A6A*) [53].

### Triggering Receptor Expressed on Myeloid Cells 2

Triggering receptor expressed on myeloid cells 2 (*TREM2)* gene product is an important part of transmembrane receptor-signaling complex that is very abundant on the cell surface of microglia where it plays an important role in downregulation of inflammation, microglial survival and activation, and phagocytosis [54]. There is evidence of high involvement of TREM2 in Alzheimer's disease pathology.

Different *TREM2* variants (Table 1) have been associated with Alzheimer's disease by few meta-analysis and GWAS. These variants include missense mutation rs75932628, rs6916710, rs6922617 (Table 1). *TREM2* mutations have been linked to extensive brain atrophy in Alzheimer's disease patients and with other neuropathological phenotypes characteristic for Alzheimer's disease [52].

### CD2-Associated Protein

CD2-associated protein (CD2AP) is a cytoplasmic protein involved in cytoskeletal structure regulation, receptor-mediated endocytosis, intracellular trafficking, cytokinesis, cell adhesion, and apoptosis. Few GWAS pointed to *CD2AP* SNPs (rs9296559, rs9349407) as loci possibly associated with late-onset Alzheimer's disease (Table 1). SNP rs9349407 could be associated with increased neuritic plaque burden in patients with diagnosed Alzheimer's disease [55].

### Ephrin Type-A Receptor 1

Ephrin type-A receptor 1 (EPHA1) is a tyrosine kinase family member important during the nervous system development and during the formation of synapse. It binds to membrane-bound ephrin-A family ligands leading to bidirectional signaling between two adjacent cells, directing cell adhesion and migration. EPHA1 could potentially have a role in the microglial immune response in Alzheimer's disease. Two EPHA1 gene variants (rs11771145 and rs11767557) were associated with Alzheimer's disease risk (Table 1).

## Conclusion

The knowledge about the genetic background of early-onset familial Alzheimer's disease allowed detection of mutations in *APP*, *PSEN1*, and *PSEN2* as a predictive/diagnostic screening, but only for these rare cases of autosomal dominant Alzheimer's disease. In the case of late-onset Alzheimer's disease, there is still much of the heritability that remains unexplained, even though, with the help from GWAS, there are now more than 20 different identified loci that have been associated with late-onset complex Alzheimer's disease. In the case of *APOE*, the evidence from an extensive meta-analysis shows that around 75% of individuals that carry one *APOE* ε4 allele never develop Alzheimer's disease, and around 50% of individuals diagnosed with Alzheimer's disease are not the carriers of this risk allele [56]. Therefore, the use of genetic variations identified by GWAS, for more effective diagnosis of Alzheimer's disease, is still far away from the clinical application, because the contribution of these variations to the relative risk of developing Alzheimer's disease is limited. In the light of prediction and prevention of Alzheimer's disease, there is much more we can expect from the additive genetic risk scores, which combine additive effects of numerous susceptibility loci.

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