CHAPTER 9

Genetics of dementia: a focus on Alzheimer's disease

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List of abbreviations

ABCA7 ATP-binding cassette subfamily A member 7
AD Alzheimer's disease
ADAM 10 ADAM metallopeptidase domain 10
AICD intracellular cytoplasmic/C-terminal domain
APOE apolipoprotein E
APP amyloid precursor protein
Aβ amyloid-β peptide
BIN1 bridging integrator-1
CD2AP CD2-associated protein
CD33 Siglec-3
CLU clusterin
CR1 complement receptor type 1
CTFβ carboxyterminal fragment-β
CTFα carboxyterminal fragment-α
DSG2 desmoglein 2
ECHDC3 enoyl-CoA hydratase domain containing 3
EPHA1 ephrin type-A receptor
FAD familial AD
FBXL7 F-box and leucine-rich repeat protein 7
GWAS genome-wide association study
HLA-DRB1 HLA class II histocompatibility antigen, DRB1 beta chain
HLA-DRB5 HLA class II histocompatibility antigen, DRB5 beta chain
INPP5D inositol polyphosphate-5-phosphatase D
MEF2C myocyte enhancer factor 2C
MS4A membrane-spanning 4-domain family, subfamily A
MTHFD1L monofunctional C1-tetrahydrofolate synthase
NME8 NME family member 8 COBL—Cordon-bleu protein
PFDN1 Prefoldin subunit 1
PICALM phosphatidylinositol-binding clathrin assembly protein
PLCG2 phospholipase C gamma 2
PTK2K PTK2 protein tyrosine kinase 2
RANBP2 RAN binding protein 2
sAPPβ secreted amino-terminals APPβ
sAPPα secreted amino-terminals APPα
SNP single-nucleotide polymorphism

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SORL1 sortilin-related receptor 1
TREM2 triggering receptor expressed on myeloid cells 2
UNC5C Unc-5 netrin receptor C
USP6NL USP6 N-terminal-like

Introduction

Dementia is a major problem among the world's aging population, affecting more than 6.5% of people aged over 65 years and more than 22% of people over the age of 85 worldwide. In 2015, dementia was reported to affect an estimated 46.8 million people worldwide according to the World Alzheimer Report, with the incidence of dementia reaching epidemic proportions; worldwide projections are that the number of people living with dementia will reach 75 million by 2030 and 131.5 million by 2050 (Prince et al., 2015). Primary manifestations of dementia include cognitive dysfunction, significant disruptions to thoughts, and other intellectual impairments associated with a severe decline in emotional control and social behavior. Dementia can be caused by many brain-related diseases including schizophrenia, attention deficit hyperactivity disorder, Parkinson's disease, and vascular dementia. The most common and well-known cause of dementia is Alzheimer's disease (AD), which is responsible for about 70% of dementia cases. AD is a progressive neurodegenerative disease clinically characterized by gradual cognitive decline including loss of memory, orientation, and reasoning. AD is pathologically characterized by the presence of neurofibrillary tangles (NFTs) and amyloid plaques in the brain. For the last 2 decades, research on AD has been extensive; however, a simple, definitive diagnostic test has yet to be developed (Goedert & Spillantini, 2006). When AD symptoms are mild, clinical diagnosis can be quite challenging and easily overlooked (Hampel et al., 2004); it can only be diagnosed when the pathology has been clinically established, which usually occurs when progressive cognitive deficits affect a person's ability to cope with the functional demands of social or professional life. There is therefore great interest in developing a reliable method for early detection of AD (Hampel et al., 2004; Sunderland, Hampel, Takeda, Putnam, & Cohen, 2006).

To date a large and increasing number of research studies have focused on investigating biomarker candidates for AD (Bailey, 2007; Hampel et al., 2004). Several neurochemical biomarkers and biomarkers visible on magnetic resonance imaging (MRI) are being evaluated for sensitivity and specificity in the detection of AD pathology (Bailey, 2007). In addition to questions regarding the reliability of these markers, it is worth noting that the lumbar punctures necessary for extracting the cerebral spinal fluid (CSF) used for identifying biomarkers in AD are relatively invasive and not well tolerated as a screening method in elderly populations, the primary demographic presenting with AD. Imaging procedures such as MRI are also costly. Despite the large number of promising results, neurochemical and imaging-based markers have so far not been

established in routine clinical diagnoses of AD (Sunderland et al., 2006). Currently, the only definitive method of diagnosis is by postmortem biochemical analyses involving the quantification of amyloid plaques and NFTs in the affected brain regions, which remains as the "gold standard" for AD diagnosis (Dubois et al., 2007).

Genetic markers are the most promising biomarkers for AD diagnosis (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007). With continual advances in technology as well as the discovery of the human genome, genetic research has progressed exceptionally over the last 2 decades. The results of this research have shown both types of AD (early-onset and late-onset) have genetic links (Bertram, 2009) (Fig. 9.1).

Development of early-onset AD starts between 30 and 60 years of age; this is a rare form of AD affecting only 5% of all AD sufferers (Fadil et al., 2009). This form of AD is also known as familial AD (FAD) due to its high prevalence of inheritance. FAD is caused by a number of different genetic mutations in *amyloid precursor protein (APP), presenilin-1 (PSEN1)*, or *presenilin-2 (PSEN2)* genes (Goate et al., 1991; Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995). FAD genetic mutations induce increases in amyloid pathway activity, generating amyloid-β peptides (Aβ) resulting from APP cleavage by β- and γ-secretase enzymes (Fig. 9.2). Aβ accumulation and oligomerization

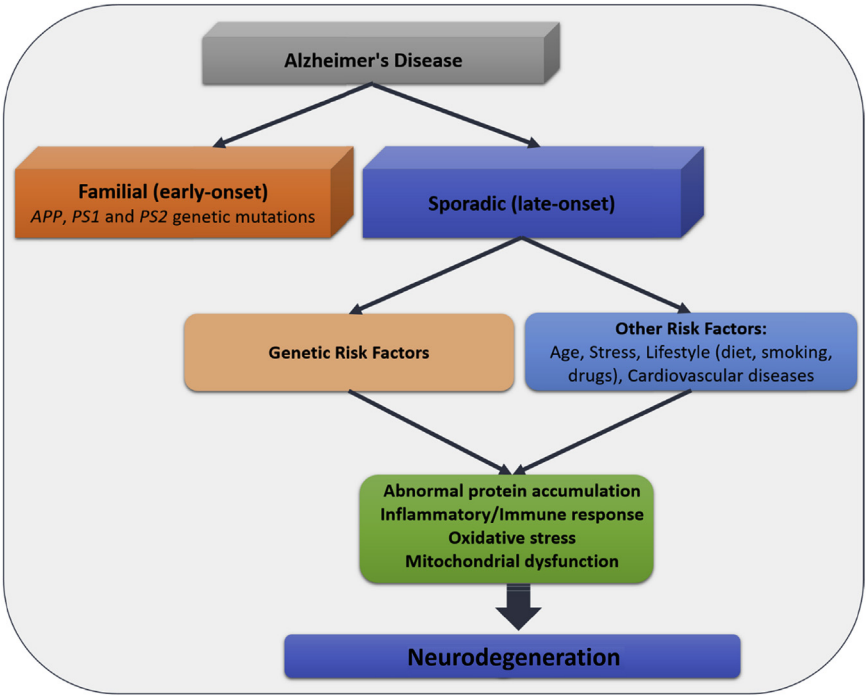

Figure 9.1 ***Risk factors for Alzheimer's disease (AD).*** In contrast to familial AD, the development of sporadic AD relies on genetic and environmental factors. A combination of genetic and other risk factors influences AD pathogenesis, resulting in neurodegenerative processes.

results in the formation of amyloid plaques in the brain (Fig. 9.2). Even if only one genetic mutation is inherited, the child will have a 50% chance of developing FAD if one parent is affected by FAD (this is classified as an autosomal-dominant genetic disease).

In most people affected by it, AD develops after 60 years of age (late-onset or sporadic AD; Fig. 9.1). Interestingly, most people suffering late-onset AD do not share the genetic mutations identified in FAD (Tanzi & Bertram, 2005). To date, over 600 genes have been proposed as "genetic risk factors" in late-onset AD, but only one of them—a form of the *apolipoprotein E* (*APOE*) gene—has been validated so far (Allen & Chiu, 2008). The *APOE* gene codes for a protein capable of assisting in the transport of cholesterol in the blood (Fig. 9.3D). Four forms/alleles of the *APOE* gene have been identified,

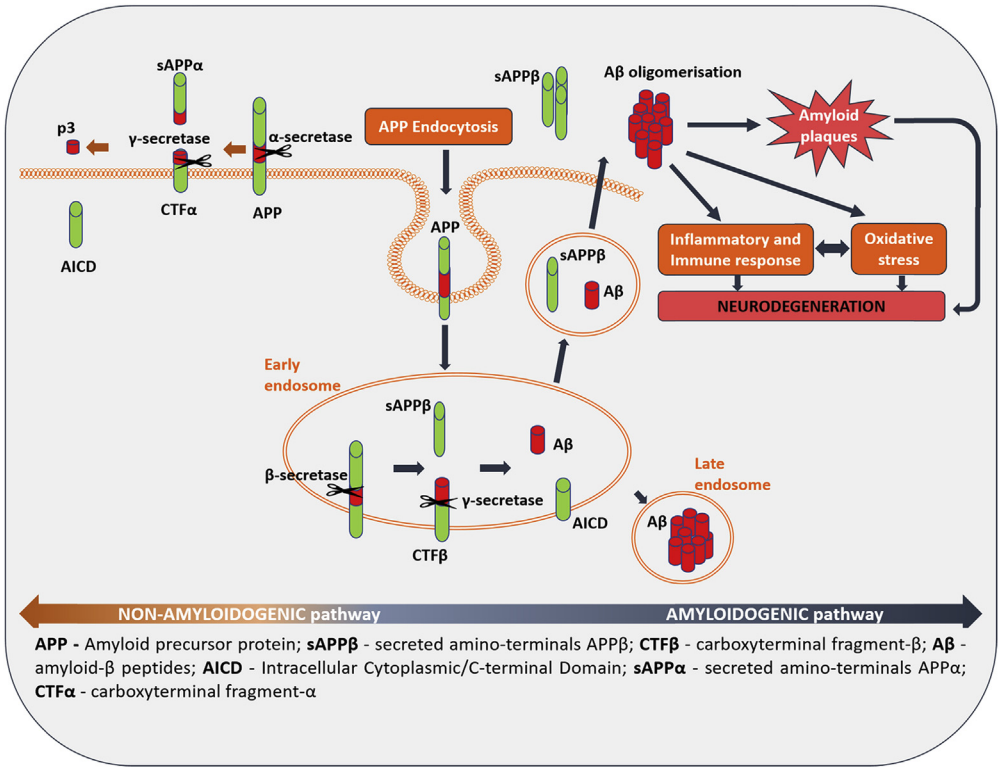

Figure 9.2 ***Amyloid precursor protein (APP) processing and its role in Alzheimer's disease (AD) pathophysiology.*** Neuronal APP can be processed through nonamyloidogenic or amyloidogenic pathways, with the latter more active in AD brains. APP is endocytosed before undergoing cleavage by β-secretase into sAPPβ and CTFβ. CTFβ is then cleaved by γ-secretase into Aβ and AICD fragments. Aβ and sAPPβ are then exocytosed back into the extracellular space. Through this process Aβ accumulates, forming oligomers, leading to the generation of amyloid plaques in the brain. The nonamyloidogenic pathway involves APP cleavage by α-secretase; this generates sAPPα and CTFα, with CTFα undergoing further cleavage by γ-secretase, resulting in p3 and AICD fragments. All by-products of this pathway are nonpathogenic.

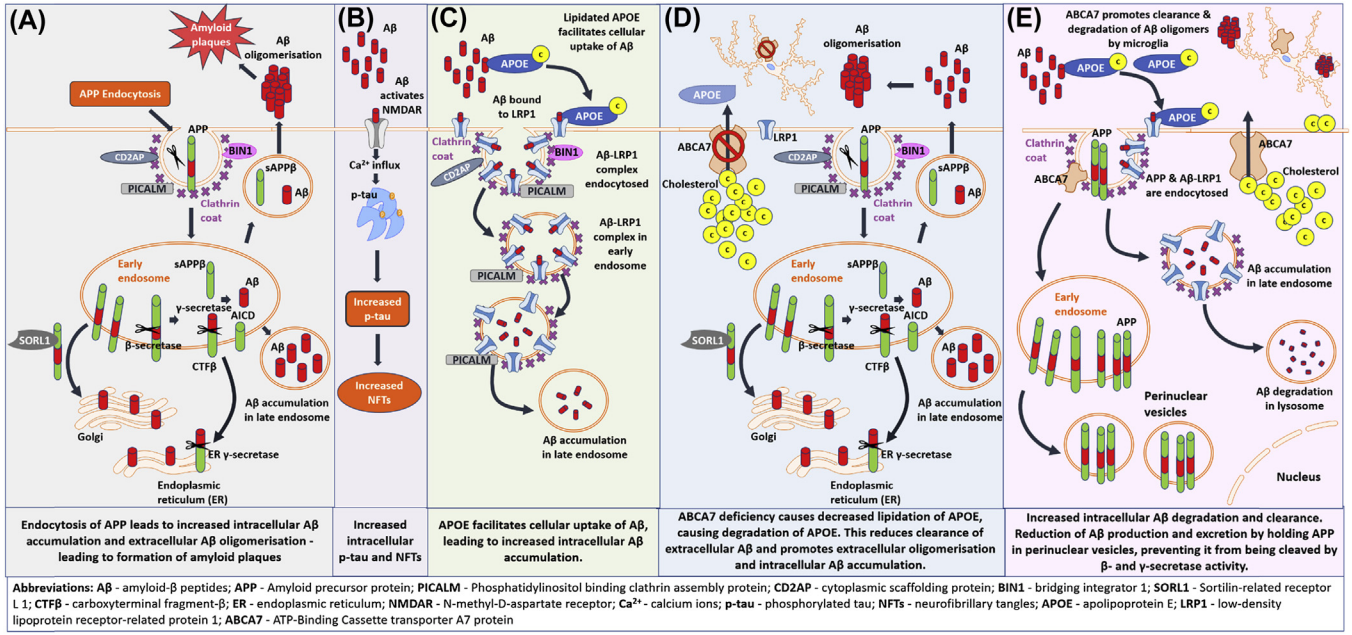

Figure 9.3 ***Mechanisms leading to imbalances of amyloid-β peptides (Aβ) and tau in Alzheimer's disease (AD) pathophysiology.*** (A) APP endocytosis plays a critical role in the accumulation of Aβ. PICALM, CD2AP, and BIN1 are clathrin-binding proteins that influence APP internalization and subsequent cleavage by early-endosomal β-secretase/γ-secretase, leading to increases in intracellular/extracellular Aβ and the production of amyloid plaques. SORL1 facilitates transport of APP from early endosomes to the Golgi for additional Aβ production. CTFβ can also be transported to the ER where it undergoes cleavage by ER γ-secretase to form Aβ. (B) Extracellular Aβ (previously secreted) can facilitate NMDAR activation leading to an influx of Ca^{2+} leading to accumulation of intracellular p-tau and production of NFTs. (C) APOE binds directly to extracellular Aβ and LRP1. Aβ—LRP1 binding initiates PICALM/clathrin-mediated endocytosis of Aβ—LRP1 complexes. After internalization PICALM remains with Aβ for trafficking. Aβ then accumulates intracellularly in endosomes. (D) ABCA7 modulates the phagocytotic activity of microglia. Dysfunction/deficiency of microglial ABCA7 reduces clearance of Aβ oligomers. Dysfunction/deficiency of neuronal ABCA7 reduces cholesterol transfer to APOE, promoting Aβ production and aggregation. (E) Expression of ABCA7 in microglia induces Aβ oligomer clearance. Neuronal ABCA7 allows transport of cholesterol across the membranes, which when binding with APOE4 facilitates Aβ uptake and degradation. ABCA7 also regulates APP processing and inhibits Aβ secretion by preventing APP cleavage.

but only *APOE* allele E4 (*APOE4*) seems to be present—in 40% of people with late-onset AD (Bu, 2009). Several studies have confirmed that *APOE4* increases the risk of developing AD, but the mechanism of how this happens is not yet understood; however, some people with *APOE4* will never develop the disease (Bu, 2009). Further research is necessary to fully understand the implications of *APOE* in the genetics of AD.

In this chapter, we discuss the genetics of late-onset AD. We first provide a quick overview of current candidate genes for late-onset AD and then propose a paradigm for the role of genes underlying cognitive processes in the genetics of AD.

Genetics of Alzheimer's disease related to its pathophysiology

Over 20,000 studies have been published on the genetics of AD so far, and more than 690 genes have been reported as associated with this pathology (Bertram et al., 2007). Genetic methodologies and analyses have advanced from pedigree-linkage and specific candidate-based association studies to genome-wide association studies (GWASs) and next-generation sequencing (NGS) (Zhu, Tan, Tan, & Yu, 2017). Although the genetic risk factors for late-onset AD are yet to be clearly established, the characterization of novel vulnerability genes for AD have facilitated our understanding of the mechanisms underlying its pathophysiology and have assisted with the development of new avenues for therapies. Here we provide a brief update of the major genes that have been identified and most strongly associated with AD (through significance in GWASs and replicated genetic studies) in relation to their roles in the pathophysiology of sporadic AD (Fig. 9.4 and Table 9.1).

Genetic linkage studies were first performed to identify chromosomal regions associated with AD, leading to the characterization of *APP*, *PSEN1*, and *PSEN2* genes in early-onset AD (Tanzi & Bertram, 2005); this subsequently led to the identification of *APOE4* as a risk factor for late-onset AD (Verghese et al., 2011). To date, *APOE4* remains the strongest genetic risk factor for sporadic AD, with the risk increasing up to 15-fold when two *APOE4* alleles are present; however, *APOE2* has been shown to be protective against AD (Giri et al., 2016). Furthermore, people with AD who carry two *APOE4* alleles have been reported to have high levels of microtubule-associated protein t-tau (total-tau) and p-tau181 (phosphorylated-tau181) in their CSF, both of which are well-established hallmarks of AD pathophysiology (Han et al., 2010) (Fig. 9.3B). *APOE* encodes for apolipoprotein E, which has a role primarily in lipid transport but can also bind to Aβ, having differential effects on the aggregation and/or clearance of Aβ depending on the APOE isoform(s) present (Fig. 9.3E). On one hand, APOE4 can inhibit Aβ clearance, leading to increased Aβ deposition in senile plaques (Kok et al., 2009) (Fig. 9.3C and D), while on the other, more highly lipidated forms of APOE (E2 and E3) are more efficient at inducing intracellular degradation of Aβ (Jiang et al., 2016). APOE4 also promotes Aβ-induced neuroinflammation and increased tau

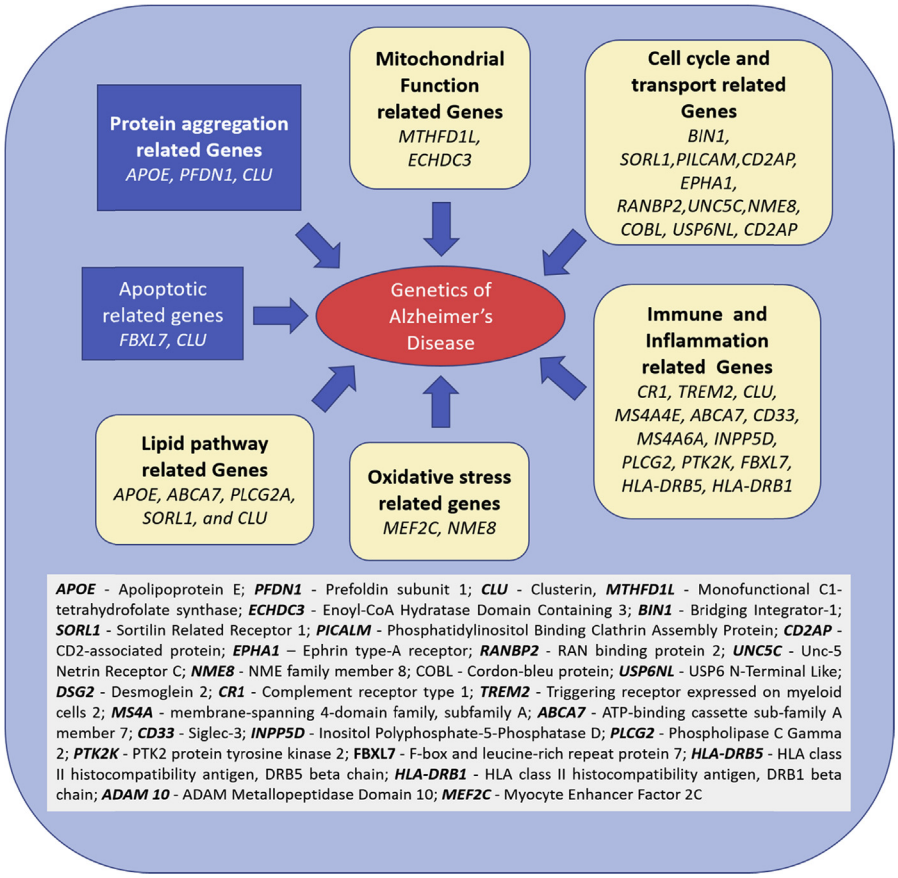

Figure 9.4 ***Genetic risk factors for sporadic Alzheimer's disease (AD).*** Summary of genes associated with sporadic AD reported by genome wide association studies ($P < 10^{-8}$) and/or replicated genetic studies, organized according to their functions in AD pathophysiology.

Table 9.1 Genes/proteins associated with Alzheimer's disease and their functions.

Gene	Location	Encoded protein	Major functions	References
CR1	1q32.2	Complement receptor 1	Aβ clearance and immune response	Zhu et al. (2017b)
TREM2	6p21.1	Triggering receptor expressed on myeloid cells 2	Immune response	Jonsson et al. (2013)
CLU	8p21.1	Clusterin	Apoptotic process, lipid pathways, inflammation, Aβ aggregation	Haight et al. (2018)

Continued

Table 9.1 Genes/proteins associated with Alzheimer's disease and their functions.—cont'd

Gene	Location	Encoded protein	Major functions	References
MS4A	11q12.2	Membrane spanning 4-domains A4E	Signal transduction, immune function	Ebbert et al. (2016)
BIN1	2q14.3	Bridging integrator 1	Vesicle mediated transport, APP trafficking transport	Chapuis et al. (2013)
FBXL7	5p15.1	F-box and leucine-rich repeat protein 7	Ubiquitination	Freudenberg-Hua et al. (2018)
PFDN1	5q31.3	Prefoldin protein 1	Stabilizes newly synthesized proteins	Freudenberg-Hua et al. (2018)
HLA-DRB	6p21.32	HLA class II beta chain paralogues	Immune response	Hamza et al. (2010)
ABCA7	19p13.3	ABC transporter member 7	Lipid transport and immune response	Steinberg et al. (2015)
MTFHD1L	6q25.1	Methylenetetrahydrofolate dehydrogenase (NADP + dependent) 1	Mitochondrial function	Freudenberg-Hua et al. (2018)
NME8	7p14.1	Thioredoxin domain-containing protein 3	Oxidation process, cell proliferation and differentiation	Liu et al. (2014)
COBL	7p12.1	Cordon-bleu WH2 repeat protein	Actin cytoskeleton and neuronal morphogenesis regulation	Freudenberg-Hua et al. (2018)
ZCWPW1	7q22.1	Zinc finger, CW type with PWWP domain 1	Epigenetic regulation	Allen et al. (2015)
USP6NL	10p14	USP6 N-terminal-like protein	Vesicle trafficking	Jun et al. (2017)
ECHDC3	10p14	Enoyl-CoA hydratase domain-containing protein 3	Mitochondrial function	Jun et al. (2017)
FRMD4	10p13	FERM domain-containing protein	Epithelial cell polarization, tauopathy	Ruiz et al. (2014)

Table 9.1 Genes/proteins associated with Alzheimer's disease and their functions.—cont'd

Gene	Location	Encoded protein	Major functions	References
CELF1	11p11-2	CUG-BP, Elav-like family	Regulation of RNA processing in the nucleus and cytoplasm	Rosenthal, Barmada, Wang, Demirci, & Kamboh, 2014
PICALM	11q14.2	Phosphatidylinositol binding clathrin assembly protein	Vesicle-mediated transport	Schjeide et al. (2011)
SORL 1	11q24.1	Sortilin-related receptor, L1	Vesicle trafficking and APP processing	Cuenco et al. (2008)
SLC24A4	14q32.12	Sodium/potassium/ calcium exchanger 4	Ion transport	Larsson et al. (2011)
BZRAP1	17q22	Benzodiazepine receptor (peripheral) associated protein 1	Neurotransmitter interactions	Freudenberg-Hua et al. (2018)
ATP5H/ KCTD2	17q25.1	ATP synthase peripheral stalk subunit H	Mitochondrial function	Boada et al. (2014)
APOE	19q13.32	Apolipoprotein E	Lipid metabolism and protein clearance/ aggregation	Roses (1996)
CD33	19q13.41	CD antigen	Vesicle-mediated transport and immune system	Bradshaw et al. (2013)
CASS4	20q13.31	Cas scaffolding protein family member 4	Cell migration and adhesion	Rosenthal et al. (2014)
CD2AP	6p12.3	CD2 associated protein	Actin cytoskeleton	Shulman et al. (2013)
DSG2	18q12.1	Desmoglein 2	Cell adhesion	Lambert et al. (2013)
INPP5D	2q37.1	Inositol polyphosphate-5-phosphatase D	Cell proliferation and survival	Lambert et al. (2013)
ADAM10	15q21.3	A disintegrin and metalloproteinase domain-containing protein 10	Protein aggregation and cell adhesion	Marioni et al. (2018)
EPHA 1	7q34	Ephrin receptor A1	Synaptic development and immune response	Lambert et al. (2013)

kinase activity (resulting in phosphorylation of tau) leading to increased neuroinflammatory response and memory deficits (Jiang et al., 2016) (Fig. 9.5).

When bound to Aβ, APOE docks to low-density lipoprotein receptor-related protein 1 (LRP1), leading to its endocytosis into the neuron in the presence of clathrin (Fig. 9.3C). Clathrin coating and protein shuffling are conducted by proteins including bridging integrator 1 (BIN1), phosphatidylinositol-binding clathrin assembly (PICALM), and CD2-associated protein (CD2), the genes for which have all been associated with late-onset AD (Table 9.1) (Freudenberg-Hua, Li, & Davies, 2018).

Seven isoforms of *BIN1* are known to be expressed in the brain, coding for membrane adaptors that form complexes with clathrin and AP2/α-adaptin, leading to synaptic vesicle endocytosis (Moustafa et al., 2018). *BIN1* expression has been reported to be elevated in postmortem AD brains and has been associated with increased tau aggregation/Aβ oligomer formation but not with Aβ expression levels in earlier stages of disease (Chapuis et al., 2013). Further investigations are necessary to clearly uncover the role of *BIN1* in AD pathophysiology.

Similarly, PICALM, which is mostly expressed in neurons, participates in clathrin-mediated endocytosis and intracellular trafficking. Single-nucleotide polymorphisms

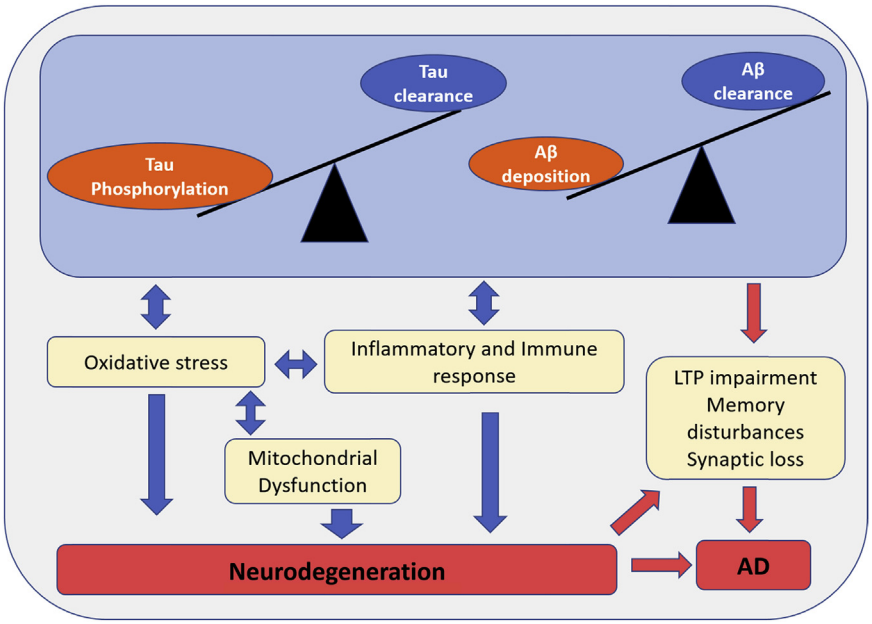

Figure 9.5 ***Pathways involved in Alzheimer's disease (AD) pathophysiology.*** An imbalance of tau and amyloid-β peptide (Aβ) accumulation induces activation of inflammatory and immune responses along with increased oxidative stress, leading to neurodegeneration. These imbalances also disturb molecular pathways underlying long-term potentiation (LTP), leading to synaptic loss and memory impairment.

(SNPs; rs3851179, rs541458) within *PICALM* have been reported as associated with a neuroprotective effect in AD (Harold et al., 2009), with SNP rs541458 being correlated with decreased levels of Aβ42 in the CSF of people with AD (Schjeide et al., 2011). PICALM is known to play a key regulatory role in the internalization of APP (Fig. 9.3C) as well as in the clearance of Aβ and tau; it is currently being investigated as a potential avenue for novel AD therapies (Zhao et al., 2015).

CD2AP encodes for the cytoplasmic scaffolding protein (CD2) involved in actin cytoskeleton regulation, intracellular trafficking and synaptic endocytosis of receptors such as epidermal growth factor receptor, and apoptosis (Lynch et al., 2003). Association between *CD2AP* SNPs (rs9296559, rs9349407) and sporadic AD has been reported in several studies (Hollingworth et al., 2011; Naj et al., 2011). Prevalence of mutations in *CD2AP* has also been correlated with the presence of amyloid plaques in AD (Hollingworth et al., 2011).

Similar to *CD2AP, MS4A6A/MS4A4E* and *CD33* are genes highly expressed in myeloid cells in the brain that have been associated with AD through GWASs (Table 9.1) and have been correlated with AD symptoms including Braak tangles and amyloid plaques (Griciuc et al., 2013; Karch et al., 2012). Neuronal membrane-spanning 4-domain family, subfamily A (MS4A) protein (also expressed in inflammatory monocytes) has been shown to have a role in the modulation of intracellular calcium, contributing to AD pathophysiology (Yu et al., 2015). The CD33 (sialic acid binding Ig-like lectin 3) protein is expressed in microglia and has significant roles in neuroinflammatory pathways and receptor-mediated endocytosis independent of clathrin (Croker et al., 2008) (Fig. 9.5). Both neuroinflammation and immune system dysfunction have been shown to have significant involvement in the pathogenesis of AD. As illustrated in Fig. 9.4, many genes that encode for inflammatory and/or immune system proteins have been characterized as having an association with AD.

CLU encodes for clusterin (apolipoprotein J), which regulates lipid transport, apoptosis, and cellular interactions. Several SNPs present in *CLU* (rs11136000, rs9331888, rs2279590, rs7982, rs7012010) have been associated with a neuroprotective effect against sporadic AD (Harold et al., 2009; Hollingworth et al., 2011; Naj et al., 2011). Since CLU can bind with Aβ and subsequently pass though the blood—brain barrier, it can modulate the aggregation and toxicity of Aβ (Weinstein et al., 2016). In contrast to CLU, *FBXL7*, which encodes for F-box and leucine-rich repeat protein 7, constitutes one of the subunits of E3 ubiquitin protein ligase and displays proapoptotic activity. A SNP in *FBXL7* (rs75002042) was associated with an increased risk of developing AD (Tosto et al., 2015). CLU also can regulate the complement system, which is highly involved in inflammatory responses. *CR1* encodes for complement receptor type 1 protein and has been associated with AD pathophysiology through genetic association, GWASs, and meta-analysis studies (Moustafa et al., 2018). Similar to CLU, the ephrin receptor A1 protein coded by *EPHA1* is highly involved in immune response. Both

rs11767557 and rs11771145 in *EPHA1* have been associated with reduced risk of late-onset AD (Hollingworth et al., 2011; Lambert et al., 2013; Naj et al., 2011).

ABCA7 encodes for ATP-binding cassette transporter A7 protein, which also has roles in regulating immune responses and lipid transport (Moustafa et al., 2018). The ABCA7 protein not only modulates the phagocytotic activity of macrophages/microglia but also reduces Aβ production and aggregation and regulates cholesterol transfer to APOE (Chan et al., 2008) (Fig, 9.3D and E). Several polymorphisms (rs3764650, rs115550680, rs4147929, rs3752246, rs142076058) have been associated with sporadic AD (Aikawa et al., 2018).

TREM2 encodes for the triggering receptor expressed on myeloid cells 2 protein, which is highly expressed on microglia and facilitates phagocytotic activity and downregulation of inflammatory responses (Jonsson et al., 2013). Mutations in *TREM2* including rs75932628 were reported to be associated with increased risk of developing late-onset AD (Jonsson et al., 2013).

Mitochondria provide the main source of energy for all cells including neurons; any dysfunction of these organelles disturbs aerobic respiratory processes and can lead to neuronal death, a characteristic symptom of AD (Hawking, 2016). Variants in the mitochondrial gene *MTHFD1L,* along with mutations in genes involved in neuronal oxidative stress *(MEF2C, NME8)*, have been associated with increased genetic susceptibility to late-onset AD (Ma et al., 2012; Moustafa et al., 2018).

Sortilin-related receptor L1 (SORL1), encoded by *SORL1,* is involved in vesicle trafficking and lipid pathways. SORL1 promotes endocytosis of APP, resulting in the generation of intraendosomal Aβ (Fig. 9.3A). Variants in this gene have been reported as associated with late-onset AD in different ethnicities and with AD symptomatology (including hippocampal atrophy and increased CSF Aβ levels) (Moustafa et al., 2018).

Decades of research and advances in molecular biology technologies and statistical analyses have allowed for the characterization of genes associated with AD (Table 9.1, Fig. 9.4). These genes can be roughly classified into six main pathways underlying AD pathophysiology and development: protein aggregation, mitochondrial dysfunction, apoptotic processes, immune/inflammatory responses, oxidative stress processes, and lipid metabolism and transport (Fig. 9.4). Despite the identification of these genetic variants in AD through linkage studies *(APOE)*, candidate gene studies/GWASs, and NGS (*TREM2, UNC5C*, a netrin receptor implicated in axonal transport, and *ADAM10* involved in increased nonamyloidogenic pathway and α-secretase activity), the heritability of sporadic AD remains to be uncovered. Several limitations have been identified in genetic linkage and candidate gene studies for sporadic AD, mainly due to small cohort sizes, false-positive outcomes, and vulnerability of locus heterogeneity. Although most genes identified in AD have failed to explain heritability for sporadic AD, they play a crucial role in gaining a better understanding of not only the genetic complexity underlying sporadic AD but also the possible molecular mechanisms responsible for the

neurodegenerative symptoms of AD. By improving the body of knowledge about AD pathophysiology and exploring AD phenotypes such as CSF biomarkers, imaging data, and neuropsychological assessments in line with identified genetic variants, potential effective therapies will be unveiled.

Memory impairment is one of the main AD endophenotypes, along with disturbances in executive functioning, language, attention, and affect. In the next section, genes associated with cognitive dysfunction in the context of AD will be briefly discussed.

Genes related to cognition involved in Alzheimer's disease

Progressive deterioration of higher order functions such as memory, affective changes, and behavioral changes (e.g., repetitive behavior) are hallmarks indicating the development of AD (Goedert & Spillantini, 2006). Memory is mediated by a set of neural mechanisms allowing individuals to encode, consolidate, retain, and retrieve information. It is a critical function providing people with a sense of self that links past, present, and future. Different memory types have been defined according to their function and nature—short-term memory versus long-term memory or implicit versus declarative memory (Kandel, 2006). Declarative memory includes semantic memory (storage of context-independent information) and episodic memory (storage of specific information related to a context, generally time and location) (Kandel, 2006). People with AD first exhibit disruption in their semantic memory, usually illustrated by the difficulty of naming items and general verbal fluency (Jahn, 2013). In the context of AD, disturbances in semantic memory reflect the presence of neuropathological dysfunction (such as loss of synaptic connections and decreases in dendritic density) in both temporal and frontal lobes (Starr et al., 2005). Located in the temporal lobe, the hippocampal formation is critical for the encoding and consolidation of information from short-term to long-term memory (Kandel, 2006). Deterioration of declarative memory in people with AD reflects damage and atrophy of the hippocampus, which occurs in the early stages of AD development (Drebing et al., 1994), whereas damage in the frontal lobes reflects disturbances in working memory (executive functioning, attention) in people with AD (Kalpouzos et al., 2005).

Damage to memory-related brain regions has been associated with gene mutations and alterations in the expression of candidate genes for sporadic AD. *APOE4* has been correlated with both episodic memory decline and atrophy of the temporal lobes (Wolk et al., 2011), particularly in the hippocampal region (Kerchner et al., 2014). *APOE4* carriers also showed decreased gray matter volume with age and increased amyloid load associated with impaired glucose metabolism; furthermore, they showed cerebral amyloid angiopathy in their temporal lobes, reflecting the struggle for local brain tissue to maintain adequate functions for cell survival (Ramanan et al., 2014). Deposition of Aβ plaques in the AD brain was also correlated with a decline in both episodic memory

and hippocampal volume (Mormino et al., 2009). Excessive accumulation of senile plaques and NFTs in the temporal lobe compared with other brain regions reflects the progression of cognitive decline in AD (Wolk et al., 2011). Interactions between *PICALM* (rs3851179) and *APOE4* were also found to be associated with cognitive impairment and temporal lobe atrophy in AD brains (Morgen et al., 2014).

Regarding immune-related genetic variants, a variant in *NME8* (rs2718058) was reported to be associated with cognitive dysfunction along with atrophy of the hippocampal region and increased CSF tau levels (Liu et al., 2014). *CD33* microglial gene expression was positively correlated with the presence of amyloid plaques and cognitive dysfunction (Griciuc et al., 2013). Interestingly, the *EPHA1* variant rs11771145 showed a protective effect against sporadic AD and was correlated with functional modifications of the hippocampal formation and temporal lobe (Wang et al., 2015).

Following whole-genome sequencing, a rare APP variant (rs63750847) was also characterized, demonstrating a neuroprotective role for AD in an elderly Icelandic population, illustrated by a decreased level of cognitive decline as well as the decreased production and aggregation of Aβ compared with that in people with AD (Jonsson et al., 2012).

Learning and memory processes are supported by molecular networks such as the glutamatergic system, including metabotropic (AMPA) and ionotropic (NMDA) receptors, which are responsible for long-term potentiation (LTP). These processes occur exclusively in the hippocampus and underlie synaptic plasticity (Kandel, 2006). The accumulation of both Aβ oligomers and phosphorylated-tau in the hippocampus has been associated with decreased LTP and dysfunctional neuronal communication (Palop & Mucke, 2010) (Fig. 9.5).

To date, many candidate gene association studies have been performed, and genetic variants have been implicated in many different genes related to neurobiological processes underlying learning and memory such as *BDNF, HTR2A, COMT, CLSTN2, KIBRA, CAMTA1*, *PSD*, and *CPEB3*. Genetic associations with AD have been previously reported for these genes that are mainly involved in neurotransmitter systems. However, for some, these associations did not retain their significance in GWAS analysis or showed controversial results in replicated studies (Rogaeva & Schmitt-Ulms, 2016). Future studies will be required for further investigating the role of cognitive-related genes in sporadic AD.

Conclusion

AD is a complex neurodegenerative disease with a strong genetic component. Here we have reviewed the main genes known to be involved in the genetic vulnerability of sporadic AD and in relation to AD pathophysiology: *APOE, BIN1, PICALM, CD2AP, MSA4A, CLU, CR1, CD 33, TREM2, FBXL7, EPHA1, MTHFD1L ABC7, MEF2C, NME8*, and *SORL1*. We have also discussed the role of some of these genes

in cognitive decline as observed in people with AD. Gaining a better understanding of the genetic profiles of people with AD in relation to their cognitive impairment and neuronal dysfunction is critical to the future design and assessment of efficient therapies for late-onset AD.

Although genetic components continue to be important risk factors for sporadic AD, this pathology remains multifactorial with complex interactions between genetic, epigenetic, and environmental factors. Epigenetic mechanisms are reversible and can alter levels of gene expression through modulation of gene transcription, leading to changes in phenotypes such as altered behaviors observed in people with AD.

Better understanding genetic and epigenetic markers for AD will allow us to predict the efficiency of therapies based on individual genetic profiles and allow for better diagnostic screening for early-stage AD. Overall, with advances in genetic technology and a better understanding of AD genetic markers, the development of future therapies for AD seems promising.

Definitions

Candidate gene studies: examining the association of one or more genetic markers in a single gene in relation to a disease and/or trait

Genes: sequence of DNA encoding specific proteins

Genetic mutations: alterations in the sequence and/or type of nucleotide in the DNA

Genetic risk factors: DNA sequence responsible for the phenotypical expression of a disease or trait

Genome-wide association studies: a study examining the entire genome (every gene from an individual) of everyone within the study (usually case—control) to determine whether specific genetic regions are associated with a disease or trait

Linkage studies: investigating the position/location of genes associated with a disease or trait relative to specific chromosomal regions within families

Sequencing: genetic technology used to identify the order of specific nucleotides of tested DNA

Single-nucleotide polymorphism: change of only *one* nucleotide in the DNA sequence

Key facts of cognition

- Cognition is the ability to integrate information from all your senses, creating a mental picture of yourself and the world around you.
- Learning, memory, attention, and the formation of knowledge are all processes involved in cognition.

- Cognitive dysfunction is disruption to thoughts, attention, learning, and memory processes and is a symptom of many disorders affecting the brain including schizophrenia, attention deficit hyperactivity disorder, epilepsy, Parkinson's disease, and Alzheimer's disease.
- The hippocampus is a seahorse-shaped brain region responsible for converting short-term memory into long-term memory.
- M. H. famously had both hippocampi removed during drastic surgery to treat severe epilepsy; he lived for over 50 years with no hippocampi, assisting researchers studying cognitive disorders for the remainder of his life.

Summary points

- This chapter focuses on providing a brief overview of genes associated with sporadic (late-onset) Alzheimer's disease (AD).
- Despite decades of research, no current and reliable test is currently available for the diagnosis of AD.
- Focus on genetic biomarkers as diagnostic tools is promising.
- Genes associated with sporadic AD through linkage, association, and genome-wide association study case studies are briefly described.
- Genes underlying cognitive function are discussed in the context of AD.

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