

Review Article

Function and Comorbidities of Apolipoprotein E in Alzheimer's Disease

Valérie Leduc,^{1,2} Dorothee Domenger,^{1,2} Louis De Beaumont,^{1,2} Daphnée Lalonde,^{1,2} Stéphanie Bélanger-Jasmin,^{1,2} and Judes Poirier^{1,2,3}

¹Department of Psychiatry, Douglas Mental Health University Institute, Perry Pavilion, E-3207.1, 6875 Lasalle Boulevard, Verdun, QC, Canada H4H1R3

²Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada H3A2B4

³McGill Centre for Studies in Aging, Verdun, QC, Canada H4H1R3

Correspondence should be addressed to Judes Poirier, judes.poirier@mcgill.ca

Received 30 November 2010; Accepted 9 February 2011

Academic Editor: Mikko Hiltunen

Copyright © 2011 Valérie Leduc et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Alzheimer's disease (AD)—the most common type of dementia among the elderly—represents one of the most challenging and urgent medical mysteries affecting our aging population. Although dominant inherited mutation in genes involved in the amyloid metabolism can elicit familial AD, the overwhelming majority of AD cases, dubbed sporadic AD, do not display this Mendelian inheritance pattern. Apolipoprotein E (APOE), the main lipid carrier protein in the central nervous system, is the only gene that has been robustly and consistently associated with AD risk. The purpose of the current paper is thus to highlight the pleiotropic roles and the structure-function relationship of APOE to stimulate both the functional characterization and the identification of novel lipid homeostasis-related molecular targets involved in AD.

1. Introduction

Cardiovascular diseases (CVDs), a group of disorders involving the heart and blood vessels, are currently the world's leading cause of death and the top ranking therapeutic category in terms of prescription drug spending. However, given the alarming aging of the population and the increase longevity of humans, Alzheimer's disease (AD) and other related dementias are set to become the next great health crusade of the coming decades [1]. Interestingly, these progressive degenerative disorders share common etiological grounds: advancing age, apolipoprotein (apo) E4 inheritance, cigarette smoking, high blood pressure, diabetes, obesity, oxidative stress, and abnormal blood cholesterol levels all concur to increase one's liability to develop CVD [2, 3] and dementias [4]. While the connection between vascular factors and cognition remains obscure, converging evidence associates the deficiency of APOE with impaired cognition (see Section 4). Importantly, APOE is the only locus known to significantly contribute to the risk of developing the late-onset form of AD, with the E4 and E2 alleles, respectively,

increasing and decreasing the risk level [5–7]. Given its pleiotropic function (see Sections 2 and 3), the mechanisms by which APOE may exert its effects remain unclear. Yet, APOE primarily functions as a major lipid transporter in the periphery and as the main one in the central nervous system (CNS), putting lipid homeostasis center stage for the maintenance of cognitive function and the promotion of AD (see Section 3). Accordingly, alterations in lipid homeostasis are known to severely impair neuronal function and elicit progressive disorders such as Farber's, Gaucher and Niemann-Pick type C diseases [8–10]. In addition to its association with AD, APOE genotype also correlates with a wide range of other dementias and neurodegenerative disorders (see Section 5). These converging findings strongly support the implication of cholesterol/lipid metabolism as a key factor in neurodegenerative disorder etiology, a concept still under-studied in the field of AD. To stimulate interest in identifying novel, lipid homeostasis-related molecular targets involved in AD pathogenesis, this paper reviews the latest advances and concepts associated with APOE functions.

2. Structural Organization and Toxicological Properties of the APOE Protein

2.1. Association between APOE and AD: Two Antipode Isoforms. The APOE gene is mapped onto chromosome 19 and mainly exists in humans as three possible isoforms differing from each other by single amino acid substitutions at positions 112 and 158. APOE isoforms are unevenly distributed in the general population as 77% of people carry the E3 allele, 15% the E4 allele, and 8% the E2 allele [5, 11]. Second only to aging, APOE is now recognized as the most important risk factor for the late-onset form of AD. Indeed, in addition to numerous case control studies [5, 6, 12] several independent genome-wide association studies (GWASs) have been performed in homogeneous and heterogeneous population of AD and age-matched control cases in North America, Europe, and Asia [13–17]. Using genome-wide statistical criterion, the APOE4 allele was found to be associated with AD in all these independent studies. Accounting for as much as 50% of the genetic variation in liability to develop AD [18], carriers of the APOE4 allele who develop AD do so at an earlier age at onset and exhibit higher levels of soluble beta-amyloid ($A\beta$) peptide, increased senile plaque (SP) [19], and neurofibrillary tangle (NFT) accumulation, as well as more extensive cholinergic deficits [20–22].

In contrast, the APOE2 variant is associated with a marked risk reduction of AD [7]. Indeed, carriers of the APOE2 allele have less AD pathological changes than APOE3 carriers, that is, less pathological $A\beta$, SP, and NFT levels [23–26], as well as larger regional cortical thicknesses and volumes indicative of greater brain reserve against cognitive decline [27]. These diametrically opposite effects of APOE4 and APOE2, which only differ by subtle amino acid substitutions at positions 112 and 158, sparked a large interest in understanding how these proteins differ at the molecular level.

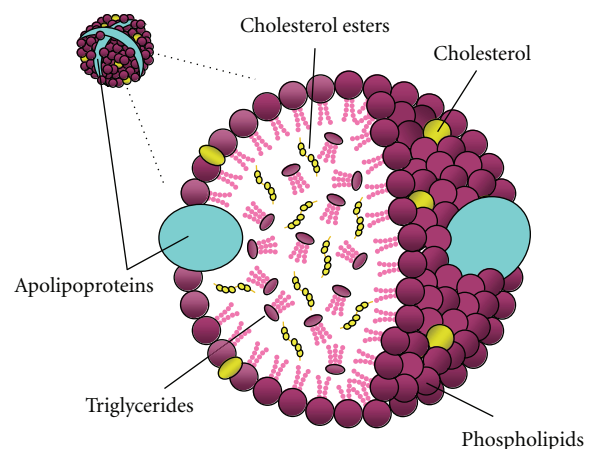
2.2. APOE Basic Structural Arrangement. APOE is a major protein constituent of plasma and CNS lipoproteins (see Box 2.2.1) and functions primarily as a lipid transporter in the human body. Through its binding to members of the low-density lipoprotein receptor (LDLR) family present on the plasma membrane, APOE effectively mediates the uptake of lipoproteins by cells [28, 29] or activate signalling pathways that modulate lipid homeostasis [30]. At physiological levels, a substantial amount of APOE is bound to lipoprotein, whereas a significant fraction of APOE could be associated with cell surface proteoglycans in a lipid-free state [31]. As will be discussed in more detail below, these lipid-bound and lipid-free conformational states likely affect the biological functions of APOE.

In the lipid-free state, the APOE protein (299 residues) is organized as two independently folded domains linked by a protease-sensitive loop (Figure 1): an N-terminal (NT) domain (residues 1–191) comprised of a four-helix bundle [32, 33] and a C-terminal (CT) domain (residues 210–299) whose structural organization has still not been elucidated

despite the crystallization of a proteolytic fragment comprising residues 223–272 [34]. The NT domain was shown to bear the LDLR binding site [28, 35–37], whereas residues within the lipid-binding CT domain mediate the lipoprotein binding [38–40] and the APOE self-association sites [31, 41, 42] (Table 1). Indeed, at physiological concentrations (micromolar), APOE exists predominantly as a tetramer [43]. Latest results indicate that, in a lipid-free state, the CT domain of APOE forms dimer, which then dimerizes further to form a tetramer [31]. However, APOE is likely to bind to lipid from its monomeric rather than tetrameric state. The transition from lipid-free to lipid-bound APOE may thus involve the formation of multiple intermediate conformational states [44].

As suggested by the initial discovery that only lipid-bound APOE binds to LDLR with high affinity [45], the structural organization of the APOE protein significantly changes when bound to lipids or lipoproteins [44, 46, 47]. Importantly, APOE adopts many lipid-bound conformations that depend on lipoprotein size [48], lipid composition [49] and on the presence of other apolipoproteins [50]. Interestingly, recent evidence indicates, however, that dipalmitoylphosphatidylcholine-(DPPC-) bound APOE adopts an alpha-helical hairpin conformation in the shape of a horseshoe, with the CT domain oriented toward the lipoprotein surface [44, 51, 52] (Figure 1). This hairpin conformation puts all the known elements of the LDLR binding site into a structural apex, potentially explaining why only lipid-bound APOE binds to LDLR with high affinity [44, 51].

2.2.1. Box 1



Lipids are hydrophobic molecules that use lipoproteins to move through aqueous environments. These lipoprotein particles comprise a nonpolar core of triglycerides (TGs) and cholesterol esters surrounded by an outer shell of phospholipids, cholesterol, and apolipoproteins that confer water solubility on the lipid constituents. In the periphery, lipoproteins are classified into four major classes on the basis of their associated apolipoproteins and their lipid content: chylomicrons, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein

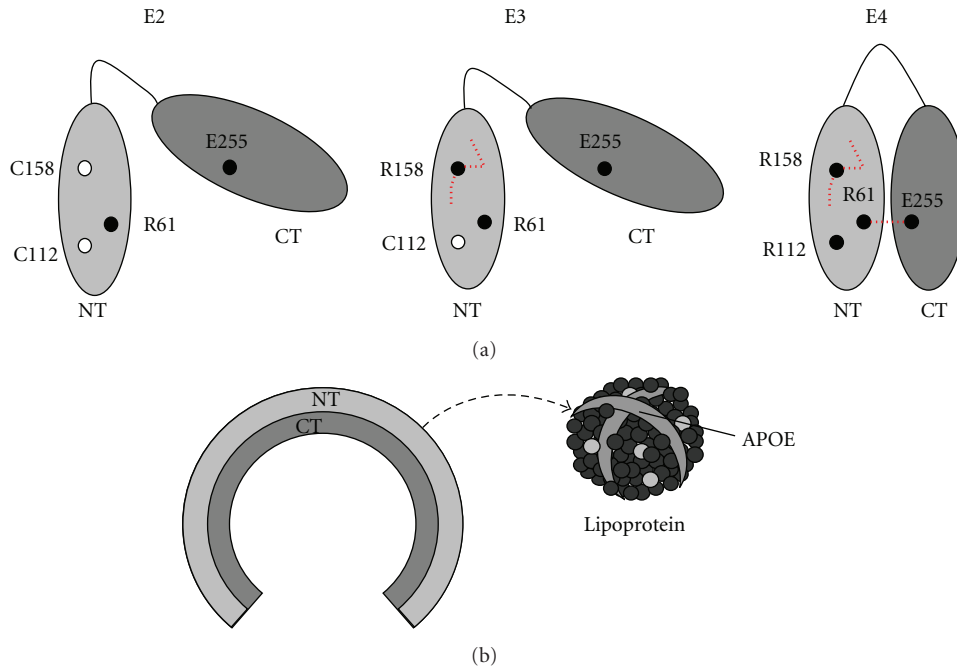


FIGURE 1: Illustration of the lipid-free (a) and DPPC-bound (b) conformational states of APOE isoforms. (a) In a lipid-free state, the NT and CT domains of APOE interact with each other. (b) The tridimensional conformation of APOE significantly changes when bound to lipid and adopts the shape of a horseshoe, with the CT domain oriented toward the lipoprotein surface. APOE or E: apolipoprotein E; the red dots line represents salt bridges; C: cysteine; R: arginine; E: glutamate; DPPC: dipalmitoylphosphatidylcholine; NT: N-terminal domain containing the low-density lipoprotein binding sites; CT: C-terminal domain comprising the lipoprotein binding and APOE self-association sites.

TABLE 1: Key structural and functional differences between the three main human APOE isoforms.

Description	E2	E3	E4
Primary sequence difference	C112 C158	C112 R158	R112 R158
Structure particularity	Disruption of salt bridge network in the NT domain		Domain interaction (creation of salt bridges R112-E109 and R61-E255)
LDLR binding	<2% normal receptor binding activity	High	High
Lipoprotein binding	HDL	HDL	VLDL/LDL
Protein stability	+++	++	+
Molten-like-globule propensity	+	++	+++

E: glutamate; C: cysteine; R: arginine; LDLR: low-density lipoprotein receptor; HDL: high-density lipoprotein; VLDL: very-low-density lipoprotein; +/++/+++ , respectively, low/medium/high.

(HDL) [53]. Chylomicrons are rich in APOB and represent the larger lipoproteins. Their function is that they carry exogenous (dietary) fatty acids from the intestine to the liver, skeletal muscles, and adipose tissues. VLDLs are assembled in the liver with TG, APOC, B, and E and ensure transport of endogenous lipids from the liver to adipose tissues. Once in the circulation, VLDLs undergo important TG hydrolysis, and their apolipoproteins (except APOB) are progressively eliminated. When cholesterol content becomes greater than the content of TG, VLDLs are converted into LDL with APOB as their main apolipoproteins. LDLs are taken up by the liver and other tissues through LDL receptor-(LDLR-) mediated

endocytosis. Finally, HDLs are the smallest but the densest lipoprotein particles because they associate with the highest proportion of apolipoproteins, mainly APOA-I. Contrary to the other lipoproteins, HDLs mediate the reverse cholesterol transport as they extract cholesterol from peripheral tissues and transport it to the liver for excretion. In the CNS, only HDL-like lipoproteins composed primarily of APOE, APOA-I, and APOJ are present [54, 55].

2.3. *Structural Arrangement and Toxicological Properties of the APOE Isoforms: Understanding the Antipodes.* The APOE

protein is polymorphic, with three common isoforms bearing identical CT domain primary structure, but distinct NT domain sequence: at positions 112 and 158, E2 has cysteines, E4 has arginines, and E3 has a cysteine and an arginine, respectively [32, 56, 57] (Figure 1, Table 1). These particularities profoundly affect the structural and functional properties of APOE (reviewed in [44]).

For instance, while APOE3 and APOE4 bind to LDLR with similar affinities, the APOE2 isoform has less than 2% of the LDLR binding activity of APOE3, at least in peripheral cells [58, 59]. This inhibition of the LDLR binding activity is mediated not only by the arginine-to-cysteine substitution at position 158, which disrupts the salt bridge network between residues R92, E96, R103, R150, D151, and D154 [33], but also by part of the CT domain [59] (Figure 1, Table 1). Consequently, a double dose of APOE2 is associated with type III dyslipidemia, a disorder characterized by increased plasma levels of cholesterol and triglycerides as well as premature CVD resulting from a defective clearance in chylomicron remnants [29, 60].

For its part, the cysteine-to-arginine substitution at position 112 in the APOE4 NT domain induces the formation of a salt bridge between arg112 and glu109, modifying the orientation of the side chain of arg61, which subsequently forms a salt bridge with glu255 in the CT domain [39] (Figure 1, Table 1). This *domain interaction* apparently influences the binding kinetics of lipid-free APOE to lipids, thereby contributing to APOE4 preferences for VLDL and LDL particles, whereas APOE3 and APOE2 isoforms preferentially bind HDL particles [38, 39, 50, 61] (Figure 1, Table 1).

As aforementioned, APOE undergoes as extensive conformational changes upon binding its ligand (lipid or lipoprotein), and the transition from lipid-free to lipid-bound APOE can be facilitated thermodynamically by the formation of intermediate, partially unfolded APOE conformational states [44]. These partially unfolded structures, also called *molten-globule-like conformations*, are believed to be crucial for lipid binding by numerous apolipoproteins, including APOE, apoAI [62], and apoAII [63]. Yet, molten-globule-like conformations are more prone to proteolysis, more vulnerable to degradation pathways and have been implicated in several diseases [44, 64]. Accordingly, the AD-associated APOE4 isoform possesses the highest propensity to form molten globule-like conformations, followed by APOE3 and finally, APOE2 [65] (Table 1). Conversely, APOE2 possesses the highest resistance to thermal and chemical denaturation, followed by APOE3 and APOE4 [66–68] (Table 1). In accordance with their disparate protein stability, APOE2 is associated with the highest levels of APOE lipoprotein, whereas APOE4 is associated with the lowest in both the blood and brain [69–72].

The lower stability of APOE4, its increased susceptibility for proteolysis as demonstrated by turnover studies in humans [73] and APOE human knockin mice [74] and its higher propensity to form molten-globule-like intermediates that actively bind to phospholipids and membranes could, in concert with fibrillar A β , promote lysosome leakage and apoptosis through lysosomal membrane disruption [75, 76]. The suboptimal features of APOE4 might also promote neu-

rototoxicity and neuroinflammation through the proteolysis of APOE4 into putative neurotoxic NT and CT fragments, a process postulated to occur solely in neurons and not in astrocytes [77]. Furthermore, this proteolytic processing of APOE is proposed to occur only in the secretory pathway, and not in the internalization pathway of neurons (i.e., there is no fragmentation of the astrocyte-derived APOE acquired by neurons following internalization of APOE-lipoproteins) [77]. However, synthesis of APOE by neurons remains to be clarified (see Section 3) through additional studies both, in model systems and in humans.

In sum, studies on the conformational structure of APOE have yielded valuable insights into the relationships that exist between the structure and function of APOE. A noteworthy finding from such studies that resulted in our further understanding of APOE4's toxicological properties is that of apoE4's domain interaction, which promotes the formation of molten-globule-like conformations. Although progress has been made toward understanding how the structural differences of the three APOE isoforms relate to phenotype and disease, much work remains to be done.

3. Biological Functions of APOE and Interaction with Its Associated Partners

3.1. An Evolutionary Perspective. APOE3 allele appears to have spread during the later stages of human evolution after originating from the ancestral APOE4 allele. According to DNA sequences representing four distinct ethnic groups, APOE3 is estimated to have spread some 225,000 years ago. The depth of the tree is estimated at 311,000 years ago (range 0.176–0.579) [78]. Although these sequences analyses do not inform us of when APOE3 originated as a mutation, they imply that APOE3 arose before anatomically modern Homo sapiens first migrated from Africa about 100,000 years ago. Thus, APOE3 was present in Neanderthals (from 300,000 years ago) and in earlier African or European Homo from which Homo sapiens is thought to have diverged. Only one APOE genotype has been reported in chimpanzees and other primate species, which closely resembles human APOE4 with arginines at positions homologous to amino acids 112 and 158 (Table 2) [79–81]. Many other mammals, including rats, mice, pigs and cows, also have arginines at these positions [80]. Given the depth of human APOE genealogy tree and the similarities between human APOE4 and mammal APOEs, the APOE4 is considered as the ancestral allele in primates [79, 80].

3.2. APOE in Cholesterol and Phospholipid Transport. APOE is the major apolipoprotein in the CNS and plays a central role in lipid transport in the nervous system [82]. The dependence of brain cells toward APOE as their chief lipid carrier and provider is emphasized by the complete absence of synthesis of other key plasma apolipoprotein such as apoA1 and apoB in the CNS [83]. In the brain, APOE is produced mainly by astrocytes [83–86] and to a lesser extent by microglia [87]. Initial studies investigating the site of APOE production in the brain suggested that only astrocytes,

TABLE 2: APOE polymorphisms in humans and species differences.

ApoE residue (+signal peptide)	Population prevalence (%)	112 (130)	158 (176)
Human			
APOE2	8	C	C
APOE3	77	C	R
APOE4	15	R	R
Chimp	100	R	R
Gorilla	100	R	R
Orangutan	100	R	R
Mice	100	R	R
Rats	100	R	R

APOE: apolipoprotein E; C: cysteine; R: arginine.

oligodendrocytes, and ependymal cells synthesized APOE [86, 88]. Under diverse physiological and pathological conditions, neurons have also been reported to express APOE, albeit at a much lower level than astrocytes, in humans [89], neuronal cell lines [90–92], mice [93], and APOE transgenic mice [94]. Surprisingly, a significant number of studies failed to observe the *synthesis* of APOE in neurons both in rodent and human brains [20, 86, 95–99]. Clearly, additional studies are needed to clarify the issue of APOE synthesis within neurons, especially since numerous studies found no evidence of APOE mRNA expression within neurons [86, 95, 100, 101].

Cholesterol homeostasis in the CNS is regulated independently from the periphery due to the presence of the blood-brain barrier (BBB) which prevents the plasma cholesterol from crossing into the CNS [102]. Maintenance of the cholesterol pool in the brain is based on the regulation of three important steps: synthesis, transport (recycling), and excretion [103]. The first step, synthesis, is provided by *de novo* anabolism that converts acetyl-CoA to cholesterol through a series of 20 complex reactions in which 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) is the rate limiting enzyme [104, 105]. While neurons of the mature brain can synthesize cholesterol, they mainly rely on astrocytes to meet their cholesterol requirements for neuronal maintenance, growth, repair and dendritic reorganization [102, 106, 107].

Recycling of lipids reflects an energy-efficient system when compared to the biosynthesis of cholesterol because the latter involves a complex pathway requiring over 20 reactions [103, 107, 108]. Cholesterol homeostasis is maintained through a series of interdependent pathways including that of cholesterol transport in which APOE is of central significance. APOE is the primary apolipoprotein in the CNS followed by APOJ (also known as Clusterin) [109], which has also been identified as a genetic risk factor in AD by genome-wide association approaches [17, 106, 110]. In the brain, APOE is produced and secreted by astrocytes and microglia and is subsequently lipidated by the ATP-binding cassette transporter A1 (ABCA1) to form lipoprotein

particles (Figure 2) [71, 102]. The role of ABCA1 is to regulate the efflux of cholesterol and phospholipids from the cell onto HDL in plasma [111]. It has been proposed that ABCA1 catalyses the initial transfer of cholesterol onto lipid-poor APOE and that ATP-binding cassette transporter G1 (ABCG1) finalizes the full lipidation of the apolipoprotein (Figure 2) [112, 113]. Although many lines of evidence support a role of ABCG1 in the regulation of cholesterol efflux, its function remains elusive. Tangier disease provides supporting evidence for the central role of ABCA1 in cholesterol homeostasis as this disease is caused by mutations in the ABCA1 gene and is characterized by HDL deficiency and cholesterol accumulation in macrophages and hepatocytes [114, 115]. Consistent with this phenomenon, ABCA1 mouse knockouts exhibit poorly lipidated APOE which in turn has been shown to influence A β metabolism [111, 116]. The pivotal role of ABCA1 in cholesterol homeostasis makes it of potent interest as a target for AD treatment.

Following lipidation, the APOE-HDL-like lipoparticles are endocytosed by specific members of the LDLR family (including LDLR, LDLR-related protein (LRP), APOER2, and the VLDLR) present on both neuronal and nonneuronal cells (Figure 2) [102, 117]. APOE endocytosis provides cholesterol to the neuron that can subsequently be used for synthesis of plasma membranes, synaptogenesis, and dendritic proliferation [118]. The functions of APOJ in lipid homeostasis and A β metabolism are very similar to those of APOE in that they are both carriers of cholesterol in the CNS and they both modulate amyloid fibrillogenesis and clearance [109, 119, 120]. Albeit their similar functions, APOE and APOJ are present on different HDL-like lipoprotein particles which differ in composition: APOJ-lipoprotein particles are lipid poor and have a higher phospholipid-to-cholesterol ratio compared to APOE-lipoprotein particles [85, 119, 121]. As well, there is some debate as to whether the cholesterol transport pathway used by APOE and APOJ differs since the receptor for APOJ, megalin/LRP-2, is not expressed by neurons and APOJ levels which are significantly increased in AD brain [122, 123] are unaltered in ABCA1 knockout mice suggesting that APOJ does not use ABCA1 for lipidation [111, 119, 124].

Excess cholesterol cannot be degraded in the brain due to its sterol ring. The predominant pathway to excrete cholesterol from the CNS is therefore to convert it into a more lipophilic 24(S)-hydroxycholesterol which can cross the BBB [112, 125]. This metabolite, only produced in neurons, is then directed to the liver where it can be excreted in the form of bile acids [126]. Other pathways account for about 36% of the excretion; however, the mechanisms remain unclear and controversial [125, 127].

APOE variants continue to receive great attention today and account for more genetic variance (25%) in cholesterol metabolism than any other gene [128]. APOE4/4 versus APOE3/3 carriers have 3 to 15% higher LDL and total cholesterol, depending on the population, diet, and exercise. APOE alleles show marked effects on blood lipids during dietary shifts. For example, in humans on a low-fat baseline diet, adding 300 mg cholesterol/day (2 egg yolks) caused serum total cholesterol to increase fourfold more in APOE4/4

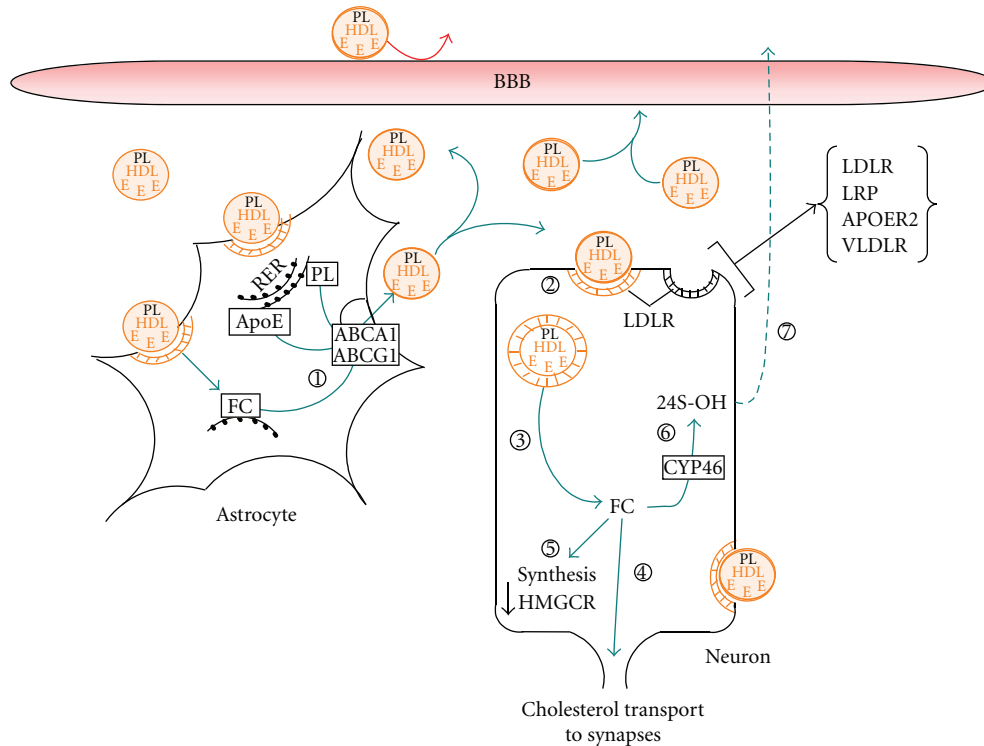


FIGURE 2: Cholesterol transport in the CNS. APOE is synthesized by astrocytes and assembles free cholesterol (FC) and phospholipids (PL) to form HDL-like particles. (1) Lipidation of these lipoparticles is facilitated via the mobilization and distribution of lipids to the cell surface by ABCA1/G1. Once secreted in the extracellular space, these HDL-like particles are directed either toward the circulation through the BBB and/or to neurons requiring lipids. (2) These APOE-HDL-like particles are recognized and endocytosed by members of the cell surface LDLR family (LDLR, LRP, APOER2, VLDLR), and (3) the FC is released within neurons and can be used for neurite elongation and/or synaptogenesis (4). As a result of lipid internalization, the endogenous synthesis of cholesterol within neurons (via the HMGCR pathway) is repressed (5). Excess cholesterol will be removed from neurons through its conversion into 24S-hydroxycholesterol (24S-OH) which is mediated by cholesterol 24S-hydroxylase (CYP46) (6). This sterol can now freely cross lipophilic membranes of the BBB and exit the brain for elimination (7). APOE or E: apolipoprotein E; BBB: blood-brain barrier; RER: rough endoplasmic reticulum; HMGCR: 3-hydroxy-3-methylglutaryl coenzyme A reductase; HDL: high-density lipoprotein; LDLR: low-density lipoprotein receptor.

carriers than in APOE3/3 and even greater relative increases of LDL cholesterol [129]. As aforementioned, APOE4 preferentially binds triglyceride-rich lipoproteins (LDL and VLDL), whereas APOE3 binds preferentially to HDL [38, 39, 50, 61]. These differences in lipoprotein binding by APOE3 and APOE4 greatly influence lipoprotein clearance and the LDL/HDL ratios, which are risk factors in cardiovascular diseases. APOE4 has smaller effects on the risk of cardiovascular disease than on AD, in the range of 10% to 50%, with effects peaking during middle age [130]. In contrast, APOE4 is the most common AD risk factor throughout the world, with a 10- to 20-fold higher risk in Caucasian homozygous E4 carriers. The impact of the APOE4 variant varies widely across different populations/ethnicities, which can likely be explained, at least partly, by an interaction between genetic and environmental factors. For example, Yorubans in Nigeria showed 70% less dementia than African Americans [131], an incidence difference which may be related to their lifelong low-fat diet.

3.3. APOE-Mediated Beta Amyloid Transport. Because the possible roles of APOE in amyloid metabolism have been

extensively reviewed recently by Kim and colleagues [106], only the potential role of APOE lipoproteins as scavengers of soluble beta amyloid ($A\beta$) peptides will be discussed in this section [21]. Indeed, evidence suggests that APOE binds avidly to soluble nonaggregated $A\beta$ fragments [6, 132]. As it was demonstrated in rat primary neuronal cell cultures, the APOE lipoproteins containing $A\beta$ may then be internalized via the APOE receptor internalization pathway [133, 134]. Following internalization, these $A\beta$ fragments could be released and degraded via the endosomal/lysosomal pathway [20, 21]. The observation that $A\beta$ reaches high intracellular concentration without affecting neuronal survival strengthens the proposed compartmentalization of internalized $A\beta$ in endosomes/lysosomes [133, 134]. Interestingly, APOE binding affinity for $A\beta$ was shown to follow an E2 > E3 > E4 gradient [135]. This provides an additional mechanism explaining, at least in part, the marked discrepancy that exists between the APOE2/E4 variants and the risk to develop AD. Indeed, the protective APOE2 variant binds $A\beta$ more avidly than the deleterious APOE4 variant and might therefore be more efficient than its APOE4 counterpart at clearing $A\beta$ fragments from the extracellular space [21].

3.4. APOE and Neuroinflammation. In addition to mediating the endocytosis of cholesterol and phospholipids into neurons, APOE have been associated with antioxidant properties in both *in vitro* and *in vivo* models [136, 137]. Additionally, in the periphery, APOE- and APOB-enriched lipoproteins are known to transport vitamin E and other lipid soluble antioxidant species [138]. Irrespective of APOE genotype, a plethora of oxidative reaction products has been found increased in the brains of AD and mild cognitive impairment subjects [139–141]. However, markers of oxidative damage are more intense in individuals who carry one or two copies of the APOE4 allele [137, 142].

As in many neurodegenerative diseases including Parkinson's disease [143], neuroinflammation caused by an abnormal activation of astrocytes and microglia is featured prominently as a pathological characteristic of AD [144–146]. This neuroinflammatory response is primarily driven locally by neuronal cell loss and extracellular A β deposits evidenced by the colocalization of numerous inflammation-related proteins (i.e., cytokines, complement receptors and acute-phase proteins), activated microglia clusters, and amyloid plaques [147, 148]. *In vitro* studies affirm that A β peptides can trigger an inflammatory response as measured by increases in standard neuroinflammatory proteins (i.e., cytokines and nitric oxide synthase) as well as nitric oxide release [149]. Neuroinflammation, especially when prolonged, is of concern for AD due to the accumulation of inflammatory molecules that are proven toxic to neurons resulting in neuronal dysfunction or death [146, 150].

As previously discussed, APOE is involved in numerous pathways influencing AD onset and progression, including A β production, clearance, and degradation as well as its role in cholesterol homeostasis. Since the initial finding of decreased inflammation from glial A β -induced APOE production [145, 151], numerous studies have reported that APOE has an anti-inflammatory function and that its stimulation by A β acts as a negative feedback system [145, 151, 152]. In support of this, APOE-deficient mice have a greater neuroinflammatory response relative to control mice [145]. *In vitro* studies also confirm that exogenously administered human APOE has the ability to attenuate A β -induced astrocyte activation as measured by a decrease in cyclo-oxygenase 2 (COX2) and inducible nitric oxide synthase [153] levels [145, 151]. However, the anti-inflammatory effect of APOE is reversed in the absence of an A β -induced inflammatory response as assessed by expression of interleukin-1b, a proinflammatory cytokine, following exogenously administered APOE [151]. Taken together these findings suggest a dual role for APOE in which it attenuates A β -induced neuroinflammation but also overproduction of APOE by this same activated glia can lead to an exacerbation of the inflammation [151, 154]. Although the mechanisms by which APOE influences the inflammatory response remain elusive, the primary candidate is the modulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) transcription and signalling pathway [147, 155, 156].

Also investigated is whether the role of APOE in neuroinflammation is affected in an isoform-specific manner. *In vivo* studies using human APOE knockin mice have shown that

following lipopolysaccharide (LPS) administration, APOE4 mice have a greater neuroinflammatory response relative to the APOE3 mice, suggesting that APOE4 has a less effective anti-inflammatory effect [157]. In addition to the decreased anti-inflammatory function of APOE4, cell culture studies investigating the proinflammatory function of APOE in the absence of A β have demonstrated that astrocytes and microglia show a greater inflammatory response when exogenous APOE4 is added compared with the APOE3 isoform [151].

Collectively, these findings imply that APOE4 has a reduced anti-inflammatory effect as well as a more vigorous proinflammatory function. Although these results infer an isoform-specific immunomodulatory effect, the efficiency of APOE2 requires further investigation.

Neuroinflammation is a prominent characteristic of AD; however, it remains uncertain whether it is promoting AD progression or merely a byproduct of the disease [148]. Numerous studies have investigated the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on AD risk and treatment [158–161]. While they remain controversial, a trend toward a decrease in AD risk is observed in population-based studies with long-term use of NSAIDs, suggesting an early role of inflammation in AD [160, 162]. Recently, the NSAID risk reduction benefits have been shown to be restricted to the apoE4 carrier subgroup in the population-based Cardiovascular Health Cognition Study [163], further highlighting the interactions linking apoE metabolism to the immune system.

4. The Neurophysiological and Functional Correlates of the APOE4 Aging Brain

4.1. Overview of APOE Functions. Acting as the main cholesterol transporter of the CNS [83], APOE plays a determinant role in neuronal maintenance, growth, repair, and reorganization [164, 165]. While CNS neurons produce just enough cholesterol to survive and grow inefficient synapses [166], a glia-derived factor consisting of cholesterol complexed to APOE-containing lipoproteins strongly promotes synapse formation [107, 167]. Indeed, the formation of multiple, highly efficient synapses in the developing CNS and in the injured adult brain was shown to be highly dependent on additional cholesterol supplies provided by the glial system [107]. It is therefore understood that the plastic properties of the brain through terminal remodeling and synaptogenesis are highly dependent on CNS cholesterol bioavailability. Needless to say that ineffective cholesterol transport associated with APOE deficiencies or deficiency in one of its most important receptors, the LDL receptor (LDLR), should invariably alter plasticity-dependent cognitive refinement and synaptic remodeling.

4.2. APOE-Deficient Mouse: A Model of Impaired Cognition. Consistent with the human APOE4/AD observations indicating the APOE levels are tightly regulated by its polymorphisms, APOE-deficient mice which express no APOE in the brain display: (a) progressive age-related

memory loss [168–174], (b) progressive loss of cortical and hippocampal synapses that reaches nearly 70% by 18 months of age [170, 173, 175], (c) a marked reduction of cholinergic activity [176], (d) impaired injury-mediated synaptic remodeling [171], (e) impaired reinnervation processes [177, 178], and (f) deterioration of phospholipids metabolism during maturation [179]. Moreover, APOE deficiency also potentiates the detrimental effects of oxidative stress on learning/memory through the expression of inflammatory proteins in the cerebral vasculature [180]. Taken together, these APOE-deficient mouse model findings, whether through oxidative stress, altered cholinergic system function, or compromised synaptic plasticity mechanisms, all corroborate the particular susceptibility of the hippocampus to APOE deficiency in mice. Strikingly, this increased vulnerability of hippocampus-related functions to APOE deficiency is consistent with disproportionate hippocampal volume atrophy in the early stages of AD [181], particularly so in carriers of the APOE4 allele [182, 183].

Similarly, in absence of LDLR, the main receptor for APOE, synaptic remodelling, and plasticity is gravely impaired in LDLR knockout (KO) mice [184]. These mice exhibit progressive age-related memory loss and significant synaptic loss in the CA1 area (–35% at 11 months) of the hippocampus [184]. Interestingly, adult LDLR KO mice expressing no brain LDLR have a 50% reduction in APOE synthesis relative to wild-type mice [185], a feature not that dissimilar from the finding that APOE4/4 AD subjects express only 50% of the normal brain APOE levels of APOE3/3 individuals [72, 186]. Relative to wild-type mice, basal hippocampal A β 1–42 are found to be significantly higher in both the LDLR KO and dual APOE/LDLR KO mice, corroborating the potential role of APOE lipoproteins as scavengers of soluble A β peptides (see Section 3). Furthermore, the fact that the APOE4 allele and LDLR genetic variations synergistically enhance the risk of developing AD by 11-fold [187] highlights the importance of both APOE synthesis and internalization in AD. Interestingly, it was shown a few years ago that cultured astrocytes from APOE4 and APOE3 human knock-in mice synthesize and release APOE to the same extent [188]. This suggests that the reported lower levels of brain APOE protein associated with the APOE4 allele might also be mediated by the internalization of APOE within brain cells. Whether the recycling and/or degradation of the APOE4–LDLR complex is differentially regulated when compared to its APOE3 counterpart warrants further studies.

Interestingly, the introduction of human APOE3 or APOE4 in the APOE KO mice completely prevents the cognitive deficit typical of these APOE-deficient mice [189, 190]. However, it should be noted that human APOE4 expression in targeted replacement mice leads over time to (a) a marked reduction of APOE levels in the brain [191], (b) compromised synaptic plasticity [192], and (c), defective cognitive performance as well as impaired long-term potentiation (LTP) [190, 193, 194]. More interestingly, cross-breeding of the humanized APOE4 or APOE3 mice with APP717 amyloid overexpressing transgenic mice almost completely prevented the characteristic accumulation of A β

deposits reported in hippocampal and cortical areas [195]. These findings are entirely consistent with the proposed notion that brain APOE acts as a local active scavenger of extracellular A β [132, 134].

4.3. APOE4 and Impaired Cognition in Nondemented Individuals. In humans, APOE4 is known to increase the risk of both familial and sporadic AD [5, 6] and to precipitate conversion to AD among mild-cognitive impairment (MCI) patients [196, 197]. MCI refers to a condition in which memory or, less commonly, another cognitive function is below normal but does not interfere with daily functioning. MCI is considered a transitional state between normal forgetfulness and AD. Moreover, converging evidence indicates that, over time, APOE4 increases the likelihood of cognitive impairments in clinically normal 50+ years old individuals [198]. Indeed, APOE4 carriers under the age of 60 years exhibited greater acceleration of age-related memory decline relative to noncarriers, despite ongoing normal clinical status [199]. This memory decline occurring prior to MCI diagnosis was previously found to be relatively specific as no differences were found in the domains of language, spatial skills, or executive function [200].

Among dominant views on what underlies this APOE4 and AD association, one is based on the observation that APOE4 proteins are the least effective in facilitating the metabolism of pathogenic A β forms, which indirectly augments A β burden [201]. Alternatively, another potent explanation for this increased risk of AD in APOE4 carriers is the deleterious effects of reduced protein expression on cholesterol homeostasis. Indeed, the APOE4 gene was shown to encode significantly less APOE proteins than E3/E2 counterparts, thereby providing insufficient levels of functional APOE4 to maintain CNS cholesterol homeostasis and neuronal health [134, 191, 193]. This notion finds compelling support in the neuroprotective properties of the APOE2 allele against late-life development of sporadic AD [24], as this APOE polymorphism is associated with a tenfold increase in APOE protein levels compared to both APOE3 and APOE4 [193]. Equally important is the demonstration that treatment of hypercholesterolemia with HMGCR inhibitors (statins), a family of lipids-lowering agents [27], in middle-aged individuals confers neuroprotection against late-life development of sporadic AD [202–204]. Furthermore, treatment by statins resulted in selective improvement of AD-prone hippocampal and frontal-related cognitive functions in APOE4 carriers, but without affecting CSF A β 42 or total tau levels [205]. Further studies are clearly needed to assess the impact of different statin therapy regimens on histopathological hallmarks of AD-like A β metabolism and tau deposition.

4.4. APOE4 Effects on Hippocampal/Entorhinal Cortex Imaging and Volume Measurements. Alongside the association between APOE4 and cognitive alterations mostly in the sphere of memory among nondemented individuals, neuroimaging studies have provided significant structural as well as functional evidence of medial temporal lobe alterations

in APOE4 carriers. While structural neuroimaging studies have yielded mixed results over the past decade, recent years have witnessed significant advances in our ability to image structural atrophy using techniques such as diffusion tensor imaging (DTI) and voxel-based morphometry (VBM). A VBM study that compared gray matter density between cognitively intact APOE4/E3 carriers and APOE3 homozygotes of all ages (age 19 to 80) showed reduced gray matter density in carriers of the APOE4 allele in right medial temporal and bilateral frontotemporal regions [206]. Another study demonstrated that the presence of an APOE4 allele in non-demented older adults was also associated with decreases in cognition joint with white/gray matter changes in the medial temporal cortex using VBM and DTI [207]. A similar VBM study more recently demonstrated that late-onset AD patients displayed a selective pattern of parahippocampal white matter loss, while early-onset AD patients experienced a more widespread pattern of posterior white matter atrophy. Among both AD groups, APOE4 positivity was associated with a greater parahippocampal white matter loss, supporting the contention that the APOE4 effect is restricted to parahippocampal white matter regions and not related to age of onset [208]. In MCI patients, left hippocampus grey matter atrophy was found to exert a stronger effect than the right hippocampus or bilateral basal forebrain in the prediction of amnesic MCI occurrence, and this left hippocampal atrophy was accentuated in APOE4 carriers relative to noncarriers [209]. This hippocampus-specific pattern of cerebral atrophy was also found in mild AD APOE4 carriers as opposed to APOE4 noncarriers who tended to exhibit greater frontoparietal atrophy [210]. In parallel, an emerging AD Neuroimaging Initiative (ADNI) study showed that APOE4 positive amnesic MCI patients with more brain atrophy were at greatest risk of functional degradation [211], highlighting the value of genetic and volumetric MRI information as predictors of disease conversion to AD.

Recent extensions to these volumetric studies described the implication of the APOE gene on brain atrophy in relation with AD cerebrospinal fluid (CSF) biomarkers levels at different disease stages. This emerging line of research finds compelling support in the recent ADNI-derived demonstration that the APOE gene reached genome-wide significance for association with CSF levels of both A β (1–42) and tau [212]. Interestingly, another ADNI study looking to define the genetic backgrounds to normal cognition, MCI (AD disease stages), and AD in relation to CSF levels found lower CSF A β (1–42) levels with APOE4 gene dose in each disease stage. Moreover, AD patients who were APOE4 homozygotes exhibited elevated total-tau (t-tau) and phosphorylated-tau (p-tau) 181 levels [213]. This is consistent with previous findings of a significant age * APOE4 genotype interaction for p-tau231, isoprostane, and t-tau CSF concentrations increased with age [214]. In keeping with this notion, cognitively intact older adults with reduced CSF A β (1–42) levels were more likely to be APOE4 positive (48% versus 11% in high A β (1–42) levels older adults), to exhibit increased whole brain loss, increased ventricular expansion, and faster hippocampal atrophy rates

[215]. Similarly, APOE4-related decreased CSF A β (1–42) and increased tau concentrations were associated with significantly higher rates of brain tissue loss that were both regional as well as disease stage specific [216]. Conversely, APOE2 carriers had slower rates of hippocampal atrophy concomitant with decreased preclinical AD pathology (i.e., higher CSF levels of A β (1–42), lower CSF p-tau and t-tau concentrations) [217]. It therefore seems that along with genetics and volumetric MRI, CSF biomarkers of AD provide valuable quantitative measurements for early detection/disease progression across disease stages.

Functional neuroimaging findings in APOE4 carriers have also abounded in the last decade. A recent study conducted with non-demented older adults found an association between APOE4 and decline in regional cerebral blood flow (rCBF) over time in brain regions especially susceptible to pathological changes in AD [218]. Accelerated rates of decline in brain functions of APOE4 carriers were suggested to contribute to an increased risk of AD and a younger age at onset [218]. These findings are based on a previous experiment conducted with a group of healthy elderly subjects among whom APOE4 carriers exhibited significantly different patterns of brain activation during a nonverbal memory task. Interestingly, these differences in brain activation were not thought to reflect task difficulty, but were rather interpreted as memory-related alterations of cognitive processing that may result from subclinical incipient AD pathology and/or APOE-related neurophysiologic heterogeneity [219]. Other evidence suggests that baseline metabolic reductions in the entorhinal cortex (EC) accurately predicted the conversion from normal aging to MCI. At follow-up, those who declined showed memory impairment and hypometabolism in temporal lobe neocortex and hippocampus particularly in APOE4 carriers [198]. These convergent cognitive and neuroanatomic findings support the notion that APOE genotype modulates the clinical phenotype of AD through influence on selective brain networks [210] and highlights the influence of genetic variance on imaging, cognitive measures, and risk for AD.

In sum, findings on the role of APOE on cognition have converged to highlight its manifest involvement in AD-prone memory and learning functions. Indeed, these APOE-related cognitive alterations were found to be concomitant with reduced cerebral metabolism, impoverished neuronal interconnections as well as damaged cerebral vasculature particularly exacerbated in medial temporal brain structures. Owing to substantial technical advances made over recent years, prevention of AD could greatly benefit from our acquired ability to relate genetic variances with abnormal brain neurophysiology patterns in cognitively intact individuals.

5. APOE and Other Neurodegenerative Diseases

5.1. Other Dementias. Next to AD, one of the leading causes of neurodegenerative dementia is Lewy body dementia (LBD). As its name clearly points on, the central pathological hallmark is the cortical Lewy bodies, as opposed to the

classical Lewy bodies described in Parkinson's disease [143], which are intracytoplasmic (ubiquitin-positive) aggregates of α -synuclein that accumulates in the substantia nigra. While they contain less NFT, the majority of LBD brains contain as much SP as in AD brains [220]. Moreover, APOE4 is consistently found associated with LBD [221–223].

Frontotemporal dementia (FTD) represents a heterogeneous group of neurodegenerative disorders characterized pathologically by frontal and/or temporal lobes atrophy and their tau isoforms pattern. Indeed, while specific FTD tauopathies typically result from the pathological aggregation and phosphorylation of one or two tau protein isoforms, all 6 tau isoforms are hyperphosphorylated in AD (for a review of FTDs classification see [224]). The best known FTD-associated diseases that will be reviewed here for their associations with APOE are Pick's disease, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP).

Pick's disease (PiD) is characterized by ballooned neurons named Pick cells that are swollen due to the presence of cytoplasmic inclusions containing tau proteins (Pick bodies). APOE associations with PiD risk or age at onset are not consistently found [225, 226]. Of note, Farrer et al. reported that the APOE4 frequency is higher in PiD than in controls (but lower than in AD) and that the number of APOE4 allele copies is inversely proportional to the age at onset [227]. Consistent with results from Singleton et al. study in LBD [223], Gustafson et al. also found that the APOE4 allele frequency was higher in PiD than in controls, but with APOE4/4 and APOE2 frequencies being, respectively, lower and higher than those reported for AD [228].

The next two FTDs, CBD and PSP, are also referred to as Parkinson-plus diseases due to parkinsonism symptoms. Differential diagnostic between AD, CBD, PSP, and PD is clinically difficult. However, CBD and PSP pathologies manifest themselves in tau-positive astroglial and neuronal inclusions. CBD and PSP differ both by the form of their tau inclusions—namely, “doughnut-shaped” in CBD as opposed to “tuft-shaped” in PSP—and by their intracerebral distribution [229]. Two studies illustrate particularly well the controversy about APOE4 association with CBD. On one hand, Pickering-Brown et al. did not find any association between APOE4 and clinical expression of CBD [226]. On the other hand, Schneider et al. reported a higher APOE4 allele frequency in 11 CBD cases [230]. To date, evidence of an association between PSP and APOE genotype is scarce, mostly due to small sample size [226, 231–235]. However, a higher frequency of the APOE2 allele (but not the APOE4 allele) in PSP relative to controls was found in a Japanese population [236].

Parkinson's disease, 2nd age-related neurodegenerative disorder in importance after AD and 1st extrapyramidal disorder, is also associated with dementia. Parkinson's disease dementia (PDD) accounts for 0.2 to 0.5% of dementia cases in the general population over the age of 65 and affects 24% to 31% of PD patients [237]. The risk of dementia is 4 to 6 times higher in PD patients than in controls [238]. More than one-third of PD patients meet criteria for AD and the differential diagnostic between PDD with and without

AD is difficult [239, 240]. These results conducted to the rise of associations studies between APOE polymorphism and PD. However, these studies have yielded mixed results. While APOE polymorphism was not associated with PD in several studies [143, 241–248], others did find associations but differed in the terms of this association. Indeed, lower E4 allele frequency and higher E4 allele frequency were, respectively, associated in sporadic and familial PD with cognitive decline [249]. Dementia in PD was repetitively associated with the E4 allele [250–253] and also with the E2 allele [254]. Age at onset appeared to be modulated by APOE genotype (earlier onset E4 > E3 > E2) [251, 252, 255, 256] and by sex [257]. Moreover, two meta-analyses sought to further corroborate the association between APOE and the risk of PD and dementia in PD. The first one [258] confirmed previous results indicating that APOE2, which is protective in AD, increases the risk of PD [254, 259]. The more recent one [260] acknowledged that APOE4 is significantly associated with an increased risk of dementia in PD but the authors warn that publication bias and heterogeneous source of data could have confounded this result.

As regard to Huntington's disease [261], another well-known neurodegenerative extrapyramidal movement disorder with neuronal intranuclear inclusion and late dementia, the APOE4 allele has been associated with a later age at onset [262], whereas the E2 and E3 alleles appear to require other factors in order to modulate age at onset [263, 264]. Finally, multiple system atrophy [265], a rare Parkinson-plus extrapyramidal disorder characterized mostly by brainstem glial Lewy body-like inclusions and subsidiary tau inclusions, has not been associated with any APOE allele [231, 232, 266].

5.2. Other Neurodegenerative Disorders. Amyotrophic lateral sclerosis (ALS), the most common motor neuron disease, also presents α -synuclein-positive inclusions, and, notably, 5% of patients will develop an FTD [267]. The association between APOE and ALS risk is controversial [268–272]. Most striking results are the association with age at onset, with the APOE4 and APOE2 alleles, respectively, decreasing [270, 272] and increasing the age [270, 273], as well as the finding that APOE plasma levels (but not APOE genotype) were correlated with a faster rate of deterioration and shortened survival time [274]. Multiple sclerosis (MS) has also been tested for its association with APOE genotype given the importance of inflammation for the disease process and the affliction of the myelin, which is vulnerable to lipid deficiency. There is a relative agreement on the negative effect of the APOE4 allele on disease severity and progression rate [275–279], but a single cross-sectional study showed that homozygosity for this allele increases both the risk for and the rate of progression of MS [280]. Contradictory results to these reported findings have also been published [241, 265, 278, 281–284].

The last neurodegenerative disease investigated in this paper section is age-related macular degeneration (ARMD). ARMD is the leading cause of vision loss in the elderly in developed countries. ARMD is associated with druse, an extracellular deposit primarily composed of activated

TABLE 3: Summary of the most common neurodegenerative diseases of the CNS, some distinctive features, and their associations with the human APOE isoforms.

Neurodegenerative disease	Pathological and clinical characteristics			APOE isoform association		
	Protein deposition	Dementia	Risk ¹	Age at onset ¹	Dementia	Severity/progression rate
AD	Extracellular amyloid- β ("SP") NCI tau ("NFT")	++	$\epsilon 4$ (dose effect)	$\epsilon 4 \setminus \epsilon 2$ (dose effect)		
PID	NCI tau ("Pick Body")	++	$\epsilon 4$ (4/4<, 2/2>/-AD)	$\epsilon 4 \setminus$ (dose effect)		
CBD	GCI (+NCI) tau ("doughnut")	++	$\epsilon 4$			
PSP	GCI (+NCI) tau ("tuft")	+	$\epsilon 2$			
LBD	NCI α -synuclein ("non-classical LB") (+SP, +NFT)	++	$\epsilon 4$ (4/4<, 2/2>/-AD)			$\epsilon 4 \setminus$ survival
MSA	GCI (+NCI) α -synuclein ("Papp-Lantos Body") (GCI + NCI tau)	(+)		$\epsilon 4$		
PD	NCI α -synuclein (classical LB)	+	($\epsilon 4$) $\epsilon 2$	$\epsilon 4 \setminus$ (> $\epsilon 3$ > $\epsilon 2$)		$\epsilon 4$
HD	Neuronal intranuclear huntingtin	+		$\epsilon 4$		
ALS	(NCI TDP-43)	5% FTD	$\epsilon 4$	$\epsilon 4 \setminus \epsilon 2$		
MS			4/4			$\epsilon 4 \setminus$ severity
ARMED	Extracellular amyloid- β ("drusen")		$\epsilon 4 \setminus \epsilon 2$	$\epsilon 4$ $\epsilon 2 \setminus$		

AD: Alzheimer's disease; PID: Pick's disease; CBD: Corticobasal dementia; PSP: Progressive supranuclear palsy; LBD: Lewy body dementia; MSA, multiple system atrophy; PD: Parkinson's disease; HD: Huntington's disease; ALS: Amyotrophic lateral sclerosis; MS: Multiple sclerosis; ARMED: Age-related macular degeneration; NCI: neuronal cytoplasmic inclusion; GCI: glial cytoplasmic inclusion; SP: senile plaque; NFT: neurofibrillary tangle; LB: Lewy body; ++ indicates very present, + moderately present, (+) present in a subset; ¹ the parentheses indicate that the association is less consistently found.

complement components, A β peptide, APOE, and ubiquitin. It is noteworthy that the molecular composition of the drusen is highly similar to that of the SP found in AD. Interestingly, AD and ARMD also share some cardiovascular risk factors. These evidence prompted association studies between APOE genotype and ARMD. Two associations were reproductively observed: the *APOE4* allele is less frequent among ARMD patients [285] and reduces the risk of developing the disease by up to 40%, whereas the *APOE2* allele is more frequent and increases the risk by up to 20% [286]. Kovács et al. stressed the opposite frequencies between *APOE4/APOE2* and ARMD/AD and highlighted the rare occurrence of ARMD among AD patients [287]. As for Baird et al., they pointed that APOE is the most consistently associated gene with ARMD. They showed that *APOE4* is protective against ARMD and/or increases its age at onset, whereas *APOE2* decreases the age at onset of ARMD [288]. Interestingly, Malek et al. presented a mouse model of ARMD in which aged human APOE transgenic mice were fed a high-fat cholesterol-rich diet [289]. They found that the mice displayed APOE isoform-dependent pathologies of different severity. Mice expressing the human *APOE4* were the most severely affected ones; they developed changes that mimicked ARMD pathology, but that could not be attributed solely to age or high-fat cholesterol-rich factors.

In sum, neurodegenerative diseases, with or without dementia, encompass a large spectrum of disorders. The more we learn about these pathologies, the more similarities and differences are found, which result in a constant reclassification of these diseases. One common pathological hallmark is the deposition of misfolded protein (amyloid- β , tau, α -synuclein, etc.). Through the modulation of disease risk, age at onset, and/or rate of progression, APOE is involved in an isoform-dependent manner in all the diseases reviewed here (Table 3). With the noticeable exception of ARMD, the *APOE4* allele is predominantly deleterious, whereas the *APOE2* is beneficial. This evidence suggests that APOE polymorphism confers a risk susceptibility not specific to AD, but to neurodegenerative disease in general.

6. Conclusion

We have reviewed the postulated roles of *APOE4* in the development of different forms of dementia and particularly, in sporadic AD. While age remains a key determinant that modulates the onset and expression of AD pathology, genetic risk factors such as *APOE4* appear to play a central role in the pathophysiology of this disease, years, if not decades, before clinical diagnosis. The combined use of genetic profiling and gene targeting will allow scientists to better target the biochemical mechanisms regulating the loss of synapses and the accumulation of amyloid deposits in the aging and diseased brain. The discovery that compounds such as estrogens, probucol, indomethacin, and even rosiglitazone can significantly induce APOE synthesis and secretion both *in vitro* and *in vivo*, and enhance cognitive performances [290–294] in small clinical trials certainly suggested a potential therapeutic role for APOE modulators

in AD. The surprising convergence of these biochemical, pharmacogenomic, and clinical observations raises exciting new possibilities and certainly interesting new therapeutic avenues for the treatment and prevention of a genetically-defined, sizeable subset of Alzheimer's disease subjects.

References

- [1] R. N. Kalaria, G. E. Maestre, R. Arizaga et al., "Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors," *The Lancet Neurology*, vol. 7, no. 9, pp. 812–826, 2008.
- [2] A. M. Miniñane, "Fatty acid-genotype interactions and cardiovascular risk," *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 82, no. 4–6, pp. 259–264, 2010.
- [3] M. Pennant, C. Davenport, S. Bayliss, W. Greenheld, T. Marshall, and C. Hyde, "Community programs for the prevention of cardiovascular disease: a systematic review," *American Journal of Epidemiology*, vol. 172, no. 5, pp. 501–516, 2010.
- [4] D. L. Dickstein, J. Walsh, H. Brautigam, S. D. Stockton, S. Gandy, and P. R. Hof, "Role of vascular risk factors and vascular dysfunction in Alzheimer's disease," *Mount Sinai Journal of Medicine*, vol. 77, no. 1, pp. 82–102, 2010.
- [5] J. Poirier, J. Davignon, D. Bouthillier, S. Kogan, P. Bertrand, and S. Gauthier, "Apolipoprotein E polymorphism and Alzheimer's disease," *The Lancet*, vol. 342, no. 8873, pp. 697–699, 1993.
- [6] W. J. Strittmatter, A. M. Saunders, D. Schmechel et al., "Apolipoprotein E: high-avidity binding to β -amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 5, pp. 1977–1981, 1993.
- [7] E. H. Corder, A. M. Saunders, N. J. Risch et al., "Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease," *Nature Genetics*, vol. 7, no. 2, pp. 180–184, 1994.
- [8] R. K. Mondal, M. Nandi, S. Datta, and M. Hira, "Disseminated lipogranulomatosis," *Indian Pediatrics*, vol. 46, no. 2, pp. 175–177, 2009.
- [9] M. Fuller, "Sphingolipids: the nexus between Gaucher disease and insulin resistance," *Lipids in Health and Disease*, vol. 9, article 113, 2010.
- [10] S. Mukherjee and F. R. Maxfield, "Lipid and cholesterol trafficking in NPC," *Biochimica et Biophysica Acta*, vol. 1685, no. 1–3, pp. 28–37, 2004.
- [11] L. A. Farrer, L. A. Cupples, J. L. Haines et al., "Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium," *Journal of the American Medical Association*, vol. 278, no. 16, pp. 1349–1356, 1997.
- [12] G. W. Rebeck, J. S. Reiter, D. K. Strickland, and B. T. Hyman, "Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions," *Neuron*, vol. 11, no. 4, pp. 575–580, 1993.
- [13] M. M. Carrasquillo, F. Zou, V. S. Pankratz et al., "Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease," *Nature Genetics*, vol. 41, no. 2, pp. 192–198, 2009.

- [14] E. M. Reiman, J. A. Webster, A. J. Myers et al., "GAB2 alleles modify Alzheimer's risk in APOE ϵ 4 carriers," *Neuron*, vol. 54, no. 5, pp. 713–720, 2007.
- [15] H. Li, S. Wetten, L. Li et al., "Candidate single-nucleotide polymorphisms from a genomewide association study of Alzheimer disease," *Archives of Neurology*, vol. 65, no. 1, pp. 45–53, 2008.
- [16] D. Harold, R. Abraham, P. Hollingworth et al., "Genomewide association study identifies variants at CLU and PICALM associated with Alzheimer's disease," *Nature Genetics*, vol. 41, no. 10, pp. 1088–1093, 2009.
- [17] J. C. Lambert, S. Heath, G. Even et al., "Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease," *Nature Genetics*, vol. 41, no. 10, pp. 1094–1099, 2009.
- [18] M. A. Pericak-Vance and J. L. Haines, "Genetic susceptibility to Alzheimer disease," *Trends in Genetics*, vol. 11, no. 12, pp. 504–508, 1995.
- [19] D. M. A. Mann, T. Iwatsubo, S. M. Pickering-Brown, F. Owen, T. C. Saido, and R. H. Perry, "Preferential deposition of amyloid β protein ($A\beta$) in the form $A\beta_{40}$ in Alzheimer's disease is associated with a gene dosage effect of the apolipoprotein E E4 allele," *Neuroscience Letters*, vol. 221, no. 2–3, pp. 81–84, 1997.
- [20] U. Beffert and J. Poirier, "Apolipoprotein E, plaques, tangles and cholinergic dysfunction in Alzheimer's disease," *Annals of the New York Academy of Sciences*, vol. 777, pp. 166–174, 1996.
- [21] J. Poirier, "Apolipoprotein E and Alzheimer's disease a role in amyloid catabolism," *Annals of the New York Academy of Sciences*, vol. 924, pp. 81–90, 2000.
- [22] M. K. P. Lai, S. W. Y. Tsang, M. Garcia-Alloza et al., "Selective effects of the APOE ϵ 4 allele on presynaptic cholinergic markers in the neocortex of Alzheimer's disease," *Neurobiology of Disease*, vol. 22, no. 3, pp. 555–561, 2006.
- [23] C. F. Lippa, T. W. Smith, A. M. Saunders, C. Hulette, D. Pulaski-Salo, and A. D. Roses, "Apolipoprotein E- ϵ 2 and Alzheimer's disease: genotype influences pathologic phenotype," *Neurology*, vol. 48, no. 2, pp. 515–519, 1997.
- [24] R. Benjamin, A. Leake, F. K. McArthur et al., "Protective effect of apoE ϵ 2 in Alzheimer's disease," *The Lancet*, vol. 344, no. 8920, pp. 473–474, 1994.
- [25] P. Tiraboschi, L. A. Hansen, E. Masliah, M. Alford, L. J. Thal, and J. Corey-Bloom, "Impact of APOE genotype on neuropathologic and neurochemical markers of Alzheimer disease," *Neurology*, vol. 62, no. 11, pp. 1977–1983, 2004.
- [26] Z. S. Nagy, M. M. Esiri, K. A. Jobst et al., "Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease," *Neuroscience*, vol. 69, no. 3, pp. 757–761, 1995.
- [27] Y. Liu, T. Paajanen, E. Westman et al., "APOE ϵ 2 allele is associated with larger regional cortical thickness and volumes," *Dementia and Geriatric Cognitive Disorders*, vol. 30, no. 3, pp. 229–237, 2010.
- [28] R. W. Mahley, "Apolipoprotein E: cholesterol transport protein with expanding role in cell biology," *Science*, vol. 240, no. 4852, pp. 622–630, 1988.
- [29] K. H. Weisgraber, A. D. Roses, and W. J. Strittmatter, "The role of apolipoprotein E in the nervous system," *Current Opinion in Lipidology*, vol. 5, no. 2, pp. 110–116, 1994.
- [30] U. Beffert, P. C. Stolt, and J. Herz, "Functions of lipoprotein receptors in neurons," *Journal of Lipid Research*, vol. 45, no. 3, pp. 403–409, 2004.
- [31] A. B. Patel, P. Khumsupan, and V. Narayanaswami, "Pyrene fluorescence analysis offers new insights into the conformation of the lipoprotein-binding domain of human apolipoprotein E," *Biochemistry*, vol. 49, no. 8, pp. 1766–1775, 2010.
- [32] C. Wilson, M. R. Wardell, K. H. Weisgraber, R. W. Mahley, and D. A. Agard, "Three-dimensional structure of the LDL receptor-binding domain of human apolipoprotein E," *Science*, vol. 252, no. 5014, pp. 1817–1822, 1991.
- [33] C. Wilson, T. Mau, K. H. Weisgraber, M. R. Wardell, R. W. Mahley, and D. A. Agard, "Salt bridge relay triggers defective LDL receptor binding by a mutant apolipoprotein," *Structure*, vol. 2, no. 8, pp. 713–718, 1994.
- [34] M. Forstner, C. Peters-Libeu, E. Contreras-Forrest et al., "Carboxyl-terminal domain of human apolipoprotein E: expression, purification, crystallization," *Protein Expression and Purification*, vol. 17, no. 2, pp. 267–272, 1999.
- [35] T. L. Innerarity, E. J. Friedlander, and S. C. Rall, "The receptor-binding domain of human apolipoprotein E. Binding of apolipoprotein E fragments," *Journal of Biological Chemistry*, vol. 258, no. 20, pp. 12341–12347, 1983.
- [36] A. Lalazar, K. H. Weisgraber, S. C. Rall et al., "Site-specific mutagenesis of human apolipoprotein E. Receptor binding activity of variants with single amino acid substitutions," *Journal of Biological Chemistry*, vol. 263, no. 8, pp. 3542–3545, 1988.
- [37] K. H. Weisgraber, T. L. Innerarity, and K. J. Harder, "The receptor-binding domain of human apolipoprotein E. Monoclonal antibody inhibition of binding," *Journal of Biological Chemistry*, vol. 258, no. 20, pp. 12348–12354, 1983.
- [38] L. M. Dong, C. Wilson, M. R. Wardell et al., "Human apolipoprotein E. Role of arginine 61 in mediating the lipoprotein preferences of the E3 and E4 isoforms," *Journal of Biological Chemistry*, vol. 269, no. 35, pp. 22358–22365, 1994.
- [39] L. M. Dong and K. H. Weisgraber, "Human apolipoprotein E4 domain interaction. Arginine 61 and glutamic acid 255 interact to direct the preference for very low density lipoproteins," *Journal of Biological Chemistry*, vol. 271, no. 32, pp. 19053–19057, 1996.
- [40] J. Dong, M. E. Balestra, Y. M. Newhouse, and K. H. Weisgraber, "Human apolipoprotein E7: lysine mutations in the carboxy-terminal domain are directly responsible for preferential binding to very low density lipoproteins," *Journal of Lipid Research*, vol. 41, no. 11, pp. 1783–1789, 2000.
- [41] L. P. Aggerbeck, J. R. Wetterau, K. H. Weisgraber, C. S. C. Wu, and F. T. Lindgren, "Human apolipoprotein E3 in aqueous solution. II. Properties of the amino- and carboxyl-terminal domains," *Journal of Biological Chemistry*, vol. 263, no. 13, pp. 6249–6258, 1988.
- [42] J. A. Westerlund and K. H. Weisgraber, "Discrete carboxyl-terminal segments of apolipoprotein E mediate lipoprotein association and protein oligomerization," *Journal of Biological Chemistry*, vol. 268, no. 21, pp. 15745–15750, 1993.
- [43] A. D. Dergunov, V. V. Shuvaev, and E. V. Yanushevskaja, "Quaternary structure of apolipoprotein E in solution: fluorimetric, chromatographic and immunochemical studies," *Biological Chemistry Hoppe-Seyler*, vol. 373, no. 6, pp. 323–331, 1992.
- [44] D. M. Hatters, C. A. Peters-Libeu, and K. H. Weisgraber, "Apolipoprotein E structure: insights into function," *Trends in Biochemical Sciences*, vol. 31, no. 8, pp. 445–454, 2006.

- [45] T. L. Innerarity, R. E. Pitas, and R. W. Mahley, "Binding of arginine-rich (E) apoprotein after recombination with phospholipid vesicles to the low density lipoprotein receptors of fibroblasts," *Journal of Biological Chemistry*, vol. 254, no. 10, pp. 4186–4190, 1979.
- [46] H. Saito, P. Dhanasekaran, F. Baldwin, K. H. Weisgraber, S. Lund-Katz, and M. C. Phillips, "Lipid binding-induced conformational change in human apolipoprotein E. Evidence for two lipid-bound states on spherical particles," *Journal of Biological Chemistry*, vol. 276, no. 44, pp. 40949–40954, 2001.
- [47] H. Saito, P. Dhanasekaran, D. Nguyen, P. Holvoet, S. Lund-Katz, and M. C. Phillips, "Domain structure and lipid interaction in human apolipoproteins A-I and E, a general model," *Journal of Biological Chemistry*, vol. 278, no. 26, pp. 23227–23232, 2003.
- [48] S. H. Gianturco, A. M. Gotto, S. L. C. Hwang et al., "Apolipoprotein E mediates uptake of S_f 100–400 hypertriglyceridemic very low density lipoproteins by the low density lipoprotein receptor pathway in normal human fibroblasts," *Journal of Biological Chemistry*, vol. 258, no. 7, pp. 4526–4533, 1983.
- [49] Y. Ishikawa, C. J. Fielding, and P. E. Fielding, "A change in apolipoprotein B expression is required for the binding of apolipoprotein E to very low density lipoprotein," *Journal of Biological Chemistry*, vol. 263, no. 6, pp. 2744–2749, 1988.
- [50] K. H. Weisgraber, R. W. Mahley, R. C. Kowal, J. Herz, J. L. Goldstein, and M. S. Brown, "Apolipoprotein C-I modulates the interaction of apolipoprotein E with β -migrating very low density lipoproteins (β -VLDL) and inhibits binding of β -VLDL to low density lipoprotein receptor-related protein," *Journal of Biological Chemistry*, vol. 265, no. 36, pp. 22453–22459, 1990.
- [51] C. A. Peters-Libeu, Y. Newhouse, D. M. Hatters, and K. H. Weisgraber, "Model of biologically active apolipoprotein E bound to dipalmitoylphosphatidylcholine," *Journal of Biological Chemistry*, vol. 281, no. 2, pp. 1073–1079, 2006.
- [52] D. M. Hatters, J. C. Voss, M. S. Budamagunta, Y. N. Newhouse, and K. H. Weisgraber, "Insight on the molecular envelope of lipid-bound apolipoprotein E from electron paramagnetic resonance spectroscopy," *Journal of Molecular Biology*, vol. 386, no. 1, pp. 261–271, 2009.
- [53] T. N. Tulenko and A. E. Sumner, "The physiology of lipoproteins," *Journal of Nuclear Cardiology*, vol. 9, no. 6, pp. 638–649, 2002.
- [54] J. E. Vance and H. Hayashi, "Formation and function of apolipoprotein E-containing lipoproteins in the nervous system," *Biochimica et Biophysica Acta*, vol. 1801, no. 8, pp. 806–818, 2010.
- [55] C. Yu, K. L. Youmans, and M. J. LaDu, "Proposed mechanism for lipoprotein remodeling in the brain," *Biochimica et Biophysica Acta*, vol. 1801, no. 8, pp. 819–823, 2010.
- [56] J. R. Wetterau, L. P. Aggerbeck, S. C. Rall, and K. H. Weisgraber, "Human apolipoprotein E3 in aqueous solution. 1. Evidence for two structural domains," *Journal of Biological Chemistry*, vol. 263, no. 13, pp. 6240–6248, 1988.
- [57] K. H. Weisgraber, "Apolipoprotein E: structure-function relationships," *Advances in Protein Chemistry*, vol. 45, pp. 249–302, 1994.
- [58] K. H. Weisgraber, T. L. Innerarity, and R. W. Mahley, "Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine-arginine interchange at a single site," *Journal of Biological Chemistry*, vol. 257, no. 5, pp. 2518–2521, 1982.
- [59] L. M. Dong, T. L. Innerarity, K. S. Arnold, Y. M. Newhouse, and K. H. Weisgraber, "The carboxyl terminus in apolipoprotein E2 and the seven amino acid repeat in apolipoprotein E-Leiden: role in receptor-binding activity," *Journal of Lipid Research*, vol. 39, no. 6, pp. 1173–1180, 1998.
- [60] R. W. Mahley, Y. Huang, and S. C. Rall Jr., "Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia): questions, quandaries, and paradoxes," *Journal of Lipid Research*, vol. 40, no. 11, pp. 1933–1949, 1999.
- [61] D. M. Hatters, M. S. Budamagunta, J. C. Voss, and K. H. Weisgraber, "Modulation of apolipoprotein E structure by domain interaction: differences in lipid-bound and lipid-free forms," *Journal of Biological Chemistry*, vol. 280, no. 40, pp. 34288–34295, 2005.
- [62] O. Gursky and D. Atkinson, "Thermal unfolding of human high-density apolipoprotein A-1: implications for a lipid-free molten globular state," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 7, pp. 2991–2995, 1996.
- [63] O. Gursky and D. Atkinson, "High- and low-temperature unfolding of human high-density apolipoprotein A-2," *Protein Science*, vol. 5, no. 9, pp. 1874–1882, 1996.
- [64] C. M. Dobson, B. E. P. Swoboda, M. Joniau, and C. Weissman, "The structural basis of protein folding and its links with human disease," *Philosophical Transactions of the Royal Society B*, vol. 356, no. 1406, pp. 133–145, 2001.
- [65] J. A. Morrow, D. M. Hatters, B. Lu et al., "Apolipoprotein E4 forms a molten globule: a potential basis for its association with disease," *Journal of Biological Chemistry*, vol. 277, no. 52, pp. 50380–50385, 2002.
- [66] J. A. Morrow, M. L. Segall, S. Lund-Katz et al., "Differences in stability among the human apolipoprotein E isoforms determined by the amino-terminal domain," *Biochemistry*, vol. 39, no. 38, pp. 11657–11666, 2000.
- [67] P. Acharya, M. L. Segall, M. Zaiou et al., "Comparison of the stabilities and unfolding pathways of human apolipoprotein E isoforms by differential scanning calorimetry and circular dichroism," *Biochimica et Biophysica Acta*, vol. 1584, no. 1, pp. 9–19, 2002.
- [68] V. Clément-Collin, A. Barbier, A. D. Dergunov et al., "The structure of human apolipoprotein E2, E3 and E4 in solution. 2. Multidomain organization correlates with the stability of apoE structure," *Biophysical Chemistry*, vol. 119, no. 2, pp. 170–185, 2006.
- [69] G. Utermann, N. Pruin, and A. Steinmetz, "Polymorphism of apolipoprotein E. III. Effect of a single polymorphic gene locus on plasma lipid levels in man," *Clinical Genetics*, vol. 15, no. 1, pp. 63–72, 1979.
- [70] G. Utermann, "Apolipoprotein E mutants, hyperlipidemia and arteriosclerosis," *Advances in Experimental Medicine and Biology*, vol. 183, pp. 173–188, 1985.
- [71] J. Poirier, "Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease," *Neurobiology of Aging*, vol. 26, no. 3, pp. 355–361, 2005.
- [72] U. Beffert, J. S. Cohn, C. Petit-Turcotte et al., "Apolipoprotein E and β -amyloid levels in the hippocampus and frontal cortex of Alzheimer's disease subjects are disease-related and apolipoprotein E genotype dependent," *Brain Research*, vol. 843, no. 1-2, pp. 87–94, 1999.
- [73] R. E. Gregg, L. A. Zech, and E. J. Schaefer, "Abnormal in vivo metabolism of apolipoprotein E in humans," *Journal of Clinical Investigation*, vol. 78, no. 3, pp. 815–821, 1986.

- [74] D. R. Riddell, H. Zhou, K. Atchison et al., "Impact of Apolipoprotein E (ApoE) polymorphism on brain ApoE levels," *Journal of Neuroscience*, vol. 28, no. 45, pp. 11445–11453, 2008.
- [75] Z. S. Ji, R. Dennis Miranda, Y. M. Newhouse, K. H. Weisgraber, H. Huang, and R. W. Mahley, "Apolipoprotein E4 potentiates amyloid β peptide-induced lysosomal leakage and apoptosis in neuronal cells," *Journal of Biological Chemistry*, vol. 277, no. 24, pp. 21821–21828, 2002.
- [76] Z. S. Ji, K. Müllendorff, I. H. Cheng, R. D. Miranda, Y. Huang, and R. W. Mahley, "Reactivity of apolipoprotein E4 and amyloid β peptide: lysosomal stability and neurodegeneration," *Journal of Biological Chemistry*, vol. 281, no. 5, pp. 2683–2692, 2006.
- [77] W. J. Brecht, F. M. Harris, S. Chang et al., "Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice," *Journal of Neuroscience*, vol. 24, no. 10, pp. 2527–2534, 2004.
- [78] S. M. Fullerton, A. G. Clark, K. M. Weiss et al., "Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism," *American Journal of Human Genetics*, vol. 67, no. 4, pp. 881–900, 2000.
- [79] R. W. Mahley and S. C. Rall, "Apolipoprotein E: far more than a lipid transport protein," *Annual Review of Genomics and Human Genetics*, vol. 1, no. 2000, pp. 507–537, 2000.
- [80] C. S. Hanlon and D. C. Rubinsztein, "Arginine residues at codons 112 and 158 in the apolipoprotein E gene correspond to the ancestral state in humans," *Atherosclerosis*, vol. 112, no. 1, pp. 85–90, 1995.
- [81] C. E. Finch and R. M. Sapolsky, "The evolution of Alzheimer disease, the reproductive schedule, and apoE isoforms," *Neurobiology of Aging*, vol. 20, no. 4, pp. 407–428, 1999.
- [82] V. Leduc, S. Jasmin-Bélanger, and J. Poirier, "APOE and cholesterol homeostasis in Alzheimer's disease," *Trends in Molecular Medicine*, vol. 16, no. 10, pp. 469–477, 2010.
- [83] R. E. Pitas, J. K. Boyles, S. H. Lee, D. Hui, and K. H. Weisgraber, "Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B_E(LDL) receptors in the brain," *Journal of Biological Chemistry*, vol. 262, no. 29, pp. 14352–14360, 1987.
- [84] E. S. Krul and J. Tang, "Secretion of apolipoprotein E by an astrocytoma cell line," *Journal of Neuroscience Research*, vol. 32, no. 2, pp. 227–238, 1992.
- [85] R. B. DeMattos, R. P. Brendza, J. E. Heuser et al., "Purification and characterization of astrocyte-secreted apolipoprotein E and J-containing lipoproteins from wild-type and human apoE transgenic mice," *Neurochemistry International*, vol. 39, no. 5-6, pp. 415–425, 2001.
- [86] J. Poirier, M. Hess, P. C. May, and C. E. Finch, "Astrocytic apolipoprotein E mRNA and GFAP mRNA in hippocampus after entorhinal cortex lesioning," *Brain Research. Molecular Brain Research*, vol. 11, no. 2, pp. 97–106, 1991.
- [87] J. S. Gong, N. Sawamura, K. Zou, J. Sakai, K. Yanagisawa, and M. Michikawa, "Amyloid β -protein affects cholesterol metabolism in cultured neurons: implications for pivotal role of cholesterol in the amyloid cascade," *Journal of Neuroscience Research*, vol. 70, no. 3, pp. 438–446, 2002.
- [88] J. K. Boyles, R. E. Pitas, and E. Wilson, "Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system," *Journal of Clinical Investigation*, vol. 76, no. 4, pp. 1501–1513, 1985.
- [89] P. T. Xu, J. R. Gilbert, H. L. Qiu et al., "Specific regional transcription of apolipoprotein E in human brain neurons," *American Journal of Pathology*, vol. 154, no. 2, pp. 601–611, 1999.
- [90] L. Dupont-Wallois, C. Soulié, N. Sergeant et al., "ApoE synthesis in human neuroblastoma cells," *Neurobiology of Disease*, vol. 4, no. 5, pp. 356–364, 1997.
- [91] S. Ferreira, M. J. Dupire, A. Delacourte, J. Najib, and M. L. Caillet-Boudin, "Synthesis and regulation of apolipoprotein E during the differentiation of human neuronal precursor NT2/D1 cells into postmitotic neurons," *Experimental Neurology*, vol. 166, no. 2, pp. 415–421, 2000.
- [92] R. M. Dekroon and P. J. Armati, "Synthesis and processing of apolipoprotein E in human brain cultures," *Glia*, vol. 33, no. 4, pp. 298–305, 2001.
- [93] U. Boschert, E. Merlo-Pich, G. Higgins, A. D. Roses, and S. Catsicas, "Apolipoprotein E expression by neurons surviving excitotoxic stress," *Neurobiology of Disease*, vol. 6, no. 6, pp. 508–514, 1999.
- [94] P. T. Xu, D. Schmechel, H. L. Qiu et al., "Sialylated human apolipoprotein E (apoE(s)) is preferentially associated with neuron-enriched cultures from APOE transgenic mice," *Neurobiology of Disease*, vol. 6, no. 1, pp. 63–75, 1999.
- [95] J. F. Diedrich, H. Minnigan, R. I. Carp et al., "Neuropathological changes in scrapie and Alzheimer's disease are associated with increased expression of apolipoprotein E and cathepsin D in astrocytes," *Journal of Virology*, vol. 65, no. 9, pp. 4759–4768, 1991.
- [96] S. H. Han, G. Einstein, K. H. Weisgraber et al., "Apolipoprotein E is localized to the cytoplasm of human cortical neurons: a light and electron microscopic study," *Journal of Neuropathology and Experimental Neurology*, vol. 53, no. 5, pp. 535–544, 1994.
- [97] F. Bao, H. Arai, S. Matsushita, S. Higuchi, and H. Sasaki, "Expression of apolipoprotein E in normal and diverse neurodegenerative disease brain," *NeuroReport*, vol. 7, no. 11, pp. 1733–1739, 1996.
- [98] R. E. Metzger, M. J. LaDu, J. B. Pan, G. S. Getz, D. E. Frail, and M. T. Falduto, "Neurons of the human frontal cortex display apolipoprotein E immunoreactivity: implications for Alzheimer's disease," *Journal of Neuropathology and Experimental Neurology*, vol. 55, no. 3, pp. 372–380, 1996.
- [99] R. E. Hartman, D. F. Wozniak, A. Nardi, J. W. Olney, L. Sartorius, and D. M. Holtzman, "Behavioral phenotyping of GFAP-ApoE3 and -ApoE4 transgenic mice: ApoE4 mice show profound working memory impairments in the absence of Alzheimer's-like neuropathology," *Experimental Neurology*, vol. 170, no. 2, pp. 326–344, 2001.
- [100] K. J. Page, R. D. Hollister, and B. T. Hyman, "Dissociation of apolipoprotein and apolipoprotein receptor response to lesion in the rat brain: an in situ hybridization study," *Neuroscience*, vol. 85, no. 4, pp. 1161–1171, 1998.
- [101] M. Nishio, E. Kohmura, T. Yuguchi et al., "Neuronal apolipoprotein E is not synthesized in neuron after focal ischemia in rat brain," *Neurological Research*, vol. 25, no. 4, pp. 390–394, 2003.
- [102] V. Hirsch-Reinshagen, B. L. Burgess, and C. L. Wellington, "Why lipids are important for Alzheimer disease?" *Molecular and Cellular Biochemistry*, vol. 326, no. 1-2, pp. 121–129, 2009.
- [103] L. A. Shobab, G. Y. R. Hsiung, and H. H. Feldman, "Cholesterol in Alzheimer's disease," *The Lancet Neurology*, vol. 4, no. 12, pp. 841–852, 2005.

- [104] G. Wójcicka, A. Jamroz-Wiśniewska, K. Horoszewicz, and J. Bętkowski, "Liver X receptors (LXRs). Part I: structure, function, regulation of activity, and role in lipid metabolism," *Postępy Higieny i Medycyny Doświadczalnej*, vol. 61, pp. 736–759, 2007.
- [105] A. Jamroz-Wiśniewska, G. Wójcicka, K. Horoszewicz, and J. Bętkowski, "Liver X receptors (LXRs). Part II: non-lipid effects, role in pathology, and therapeutic implications," *Postępy Higieny i Medycyny doświadczalnej*, vol. 61, pp. 760–785, 2007.
- [106] J. Kim, J. M. Basak, and D. M. Holtzman, "The role of apolipoprotein E in Alzheimer's disease," *Neuron*, vol. 63, no. 3, pp. 287–303, 2009.
- [107] J. Poirier, A. Baccichet, D. Dea, and S. Gauthier, "Cholesterol synthesis and lipoprotein reuptake during synaptic remodeling in hippocampus in adult rats," *Neuroscience*, vol. 55, no. 1, pp. 81–90, 1993.
- [108] J. F. Goodrum, "Cholesterol synthesis is down-regulated during regeneration of peripheral nerve," *Journal of Neurochemistry*, vol. 54, no. 5, pp. 1709–1715, 1990.
- [109] K. Sleegers, J. C. Lambert, L. Bertram, M. Cruts, P. Amouyel, and C. van Broeckhoven, "The pursuit of susceptibility genes for Alzheimer's disease: progress and prospects," *Trends in Genetics*, vol. 26, no. 2, pp. 84–93, 2010.
- [110] L. Bertram, M. B. McQueen, K. Mullin, D. Blacker, and R. E. Tanzi, "Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database," *Nature Genetics*, vol. 39, no. 1, pp. 17–23, 2007.
- [111] S. E. Wahrle, H. Jiang, M. Parsadanian et al., "ABCA1 is required for normal central nervous system apoE levels and for lipidation of astrocyte-secreted apoE," *Journal of Biological Chemistry*, vol. 279, no. 39, pp. 40987–40993, 2004.
- [112] B. L. Burgess, P. F. Parkinson, M. M. Racke et al., "ABCG1 influences the brain cholesterol biosynthetic pathway but does not affect amyloid precursor protein or apolipoprotein E metabolism in vivo," *Journal of Lipid Research*, vol. 49, no. 6, pp. 1254–1267, 2008.
- [113] W. S. Kim, A. S. Rahmanto, A. Kamili et al., "Role of ABCG1 and ABCA1 in regulation of neuronal cholesterol efflux to apolipoprotein E discs and suppression of amyloid- β peptide generation," *Journal of Biological Chemistry*, vol. 282, no. 5, pp. 2851–2861, 2007.
- [114] A. D. Attie, J. P. Kastelein, and M. R. Hayden, "Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis," *Journal of Lipid Research*, vol. 42, no. 11, pp. 1717–1726, 2001.
- [115] M. Bodzioch, E. Ors6, J. Klucken et al., "The gene encoding ATP-binding cassette transporter I is mutated in Tangier disease," *Nature Genetics*, vol. 22, no. 4, pp. 347–351, 1999.
- [116] S. E. Wahrle, H. Jiang, M. Parsadanian et al., "Deletion of Abca1 increases A β deposition in the PDAPP transgenic mouse model of Alzheimer disease," *Journal of Biological Chemistry*, vol. 280, no. 52, pp. 43236–43242, 2005.
- [117] J. Poirier, "Apolipoprotein E and cholesterol metabolism in the pathogenesis and treatment of Alzheimer's disease," *Trends in Molecular Medicine*, vol. 9, no. 3, pp. 94–100, 2003.
- [118] J. Poirier, "Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease," *Trends in Neurosciences*, vol. 17, no. 12, pp. 525–530, 1994.
- [119] A. M. Fagan, D. M. Holtzman, G. Munson et al., "Unique lipoproteins secreted by primary astrocytes from wild type, apoE (-/-), and human apoE transgenic mice," *Journal of Biological Chemistry*, vol. 274, no. 42, pp. 30001–30007, 1999.
- [120] R. P. Koldamova, I. M. Lefterov, M. I. Lefterova, and J. S. Lazo, "Apolipoprotein A-I directly interacts with amyloid precursor protein and inhibits A β aggregation and toxicity," *Biochemistry*, vol. 40, no. 12, pp. 3553–3560, 2001.
- [121] T. Nuutinen, T. Suuronen, A. Kauppinen, and A. Salminen, "Clusterin: a forgotten player in Alzheimer's disease," *Brain Research Reviews*, vol. 61, no. 2, pp. 89–104, 2009.
- [122] P. C. May, S. A. Johnson, J. Poirier, M. Lampert-Etchells, and C. E. Finch, "Altered gene expression in Alzheimer's disease brain tissue," *Canadian Journal of Neurological Sciences*, vol. 16, no. 4, pp. 473–476, 1989.
- [123] P. C. May, M. Lampert-Etchells, S. A. Johnson, J. Poirier, J. N. Masters, and C. E. Finch, "Dynamics of gene expression for a hippocampal glycoprotein elevated in Alzheimer's disease and in response to experimental lesions in rat," *Neuron*, vol. 5, no. 6, pp. 831–839, 1990.
- [124] V. Hirsch-Reinshagen, S. Zhou, B. L. Burgess et al., "Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain," *Journal of Biological Chemistry*, vol. 279, no. 39, pp. 41197–41207, 2004.
- [125] T. Vanmierlo, K. Rutten, J. Dederen et al., "Liver X receptor activation restores memory in aged AD mice without reducing amyloid," *Neurobiology of Aging*. In press.
- [126] E. G. Lund, C. Xie, T. Kotti, S. D. Turley, J. M. Dietschy, and D. W. Russell, "Knockout of the cholesterol 24-hydroxylase gene in mice reveals a brain-specific mechanism of cholesterol turnover," *Journal of Biological Chemistry*, vol. 278, no. 25, pp. 22980–22988, 2003.
- [127] C. Xie, E. G. Lund, S. D. Turley, D. W. Russell, and J. M. Dietschy, "Quantitation of two pathways for cholesterol excretion from the brain in normal mice and mice with neurodegeneration," *Journal of Lipid Research*, vol. 44, no. 9, pp. 1780–1789, 2003.
- [128] J. Davignon, R. E. Gregg, and C. F. Sing, "Apolipoprotein E polymorphism and atherosclerosis," *Arteriosclerosis*, vol. 8, no. 1, pp. 1–21, 1988.
- [129] E. Sarkkinen, M. Korhonen, A. Erkkilä, T. Ebeling, and M. Uusitupa, "Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol," *American Journal of Clinical Nutrition*, vol. 68, no. 6, pp. 1215–1222, 1998.
- [130] J. E. Eichner, S. T. Dunn, G. Perveen, D. M. Thompson, K. E. Stewart, and B. C. Stroehla, "Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review," *American Journal of Epidemiology*, vol. 155, no. 6, pp. 487–495, 2002.
- [131] H. C. Hendrie, A. Ogunniyi, K. S. Hall et al., "Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana," *Journal of the American Medical Association*, vol. 285, no. 6, pp. 739–747, 2001.
- [132] T. Wisniewski, A. Golabek, E. Matsubara, J. Ghiso, and B. Frangione, "Apolipoprotein E: binding to soluble Alzheimer's β amyloid," *Biochemical and Biophysical Research Communications*, vol. 192, no. 2, pp. 359–365, 1993.
- [133] U. Beffert, N. Aumont, D. Dea, S. Lussier-Cacan, J. Davignon, and J. Poirier, " β -amyloid peptides increase the binding and internalization of apolipoprotein E to hippocampal neurons," *Journal of Neurochemistry*, vol. 70, no. 4, pp. 1458–1466, 1998.
- [134] U. Beffert, N. Aumont, D. Dea, S. Lussier-Cacan, J. Davignon, and J. Poirier, "Apolipoprotein E isoform-specific reduction of extracellular amyloid in neuronal cultures," *Brain Research. Molecular Brain Research*, vol. 68, no. 1-2, pp. 181–185, 1999.

- [135] M. J. LaDu, M. T. Falduto, A. M. Manelli, C. A. Reardon, G. S. Getz, and D. E. Frail, "Isoform-specific binding of apolipoprotein E to β -amyloid," *Journal of Biological Chemistry*, vol. 269, no. 38, pp. 23403–23406, 1994.
- [136] M. Miyata and J. D. Smith, "Apolipoprotein E allele-specific antioxidant activity and effects on cytotoxicity by oxidative insults and β -amyloid peptides," *Nature Genetics*, vol. 14, no. 1, pp. 55–61, 1996.
- [137] K. S. Montine, S. J. Oison, V. Amarnath, W. O. Whetsell, D. G. Graham, and T. J. Montine, "Immunohistochemical detection of 4-hydroxy-2-nonenal adducts in Alzheimer's disease is associated with inheritance of APOE4," *American Journal of Pathology*, vol. 150, no. 2, pp. 437–443, 1997.
- [138] A. Bjorneboe, G. E. A. Bjorneboe, and C. A. Drevon, "Absorption, transport and distribution of vitamin E," *Journal of Nutrition*, vol. 120, no. 3, pp. 233–242, 1990.
- [139] D. A. Butterfield, J. Drake, C. Pocernich, and A. Castegna, "Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid β -peptide," *Trends in Molecular Medicine*, vol. 7, no. 12, pp. 548–554, 2001.
- [140] A. Castegna, V. Thongboonkerd, J. B. Klein, B. Lynn, W. R. Markesbery, and D. A. Butterfield, "Proteomic identification of nitrated proteins in Alzheimer's disease brain," *Journal of Neurochemistry*, vol. 85, no. 6, pp. 1394–1401, 2003.
- [141] P. Bermejo, S. Martín-Aragón, J. Benedí et al., "Peripheral levels of glutathione and protein oxidation as markers in the development of Alzheimer's disease from Mild Cognitive Impairment," *Free Radical Research*, vol. 42, no. 2, pp. 162–170, 2008.
- [142] K. S. Montine, E. Reich, M. D. Neely et al., "Distribution of reducible 4-hydroxynonenal adduct immunoreactivity in Alzheimer disease is associated with APOE genotype," *Journal of Neuropathology and Experimental Neurology*, vol. 57, no. 5, pp. 415–425, 1998.
- [143] M. Ezquerra, J. Campdelacreu, C. Gaig et al., "Lack of association of APOE and tau polymorphisms with dementia in Parkinson's disease," *Neuroscience Letters*, vol. 448, no. 1, pp. 20–23, 2008.
- [144] W. J. Streit, R. E. Mrak, and W. S. T. Griffin, "Microglia and neuroinflammation: a pathological perspective," *Journal of Neuroinflammation*, vol. 1, article 14, 2004.
- [145] M. J. LaDu, J. A. Shah, C. A. Reardon et al., "Apolipoprotein E and apolipoprotein E receptors modulate $A\beta$ -induced glial neuroinflammatory responses," *Neurochemistry International*, vol. 39, no. 5–6, pp. 427–434, 2001.
- [146] E. G. McGeer and P. L. McGeer, "The importance of inflammatory mechanisms in Alzheimer disease," *Experimental Gerontology*, vol. 33, no. 5, pp. 371–378, 1998.
- [147] J. Rogers, R. Strohmeier, C. J. Kovelowski, and R. Li, "Microglia and inflammatory mechanisms in the clearance of amyloid β peptide," *Glia*, vol. 40, no. 2, pp. 260–269, 2002.
- [148] P. Eikelenboom and W. A. van Gool, "Neuroinflammatory perspectives on the two faces of Alzheimer's disease," *Journal of Neural Transmission*, vol. 111, no. 3, pp. 281–294, 2004.
- [149] J. Hu, K. T. Akama, G. A. Krafft, B. A. Chromy, and L. J. van Eldik, "Amyloid- β peptide activates cultured astrocytes: morphological alterations, cytokine induction and nitric oxide release," *Brain Research*, vol. 785, no. 2, pp. 195–206, 1998.
- [150] L. Meda, M. A. Cassatella, G. I. Szendrei et al., "Activation of microglial cells by β -amyloid protein and interferon- γ ," *Nature*, vol. 374, no. 6523, pp. 647–650, 1995.
- [151] L. Guo, M. J. LaDu, and L. J. van Eldik, "A dual role for apolipoprotein e in neuroinflammation: anti- and pro-inflammatory activity," *Journal of Molecular Neuroscience*, vol. 23, no. 3, pp. 205–212, 2004.
- [152] M. J. LaDu, J. A. Shah, C. A. Reardon et al., "Apolipoprotein E receptors mediate the effects of β -amyloid on astrocyte cultures," *Journal of Biological Chemistry*, vol. 275, no. 43, pp. 33974–33980, 2000.
- [153] K. Uemura, A. Kuzuya, Y. Shimozone et al., "GSK3 β activity modifies the localization and function of presenilin 1," *Journal of Biological Chemistry*, vol. 282, no. 21, pp. 15823–15832, 2007.
- [154] R. Aleong, J. F. Blain, and J. Poirier, "Pro-inflammatory cytokines modulate glial apolipoprotein E secretion," *Current Alzheimer Research*, vol. 5, no. 1, pp. 33–37, 2008.
- [155] K. R. Bales, Y. Du, D. Holtzman, B. Cordell, and S. M. Paul, "Neuroinflammation and Alzheimer's disease: critical roles for cytokine/ $A\beta$ -induced glial activation, NF- κ B, and apolipoprotein E," *Neurobiology of Aging*, vol. 21, no. 3, pp. 427–432, 2000.
- [156] G. Ophir, N. Amariglio, J. Jacob-Hirsch, R. Elkon, G. Rechavi, and D. M. Michaelson, "Apolipoprotein E4 enhances brain inflammation by modulation of the NF- κ B signaling cascade," *Neurobiology of Disease*, vol. 20, no. 3, pp. 709–718, 2005.
- [157] J. R. Lynch, W. Tang, H. Wang et al., "APOE genotype and an ApoE-mimetic peptide modify the systemic and central nervous system inflammatory response," *Journal of Biological Chemistry*, vol. 278, no. 49, pp. 48529–48533, 2003.
- [158] W. A. van Gool, H. C. Weinstein, P. K. Scheltens, and G. J. M. Walstra, "Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study," *The Lancet*, vol. 358, no. 9280, pp. 455–460, 2001.
- [159] W. A. van Gool, P. S. Aisen, and P. Eikelenboom, "Anti-inflammatory therapy in Alzheimer's disease: is hope still alive?" *Journal of Neurology*, vol. 250, no. 7, pp. 788–792, 2003.
- [160] P. L. McGeer, M. Schulzer, and E. G. McGeer, "Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies," *Neurology*, vol. 47, no. 2, pp. 425–432, 1996.
- [161] P. P. Zandi and J. C. S. Breitner, "Do NSAIDs prevent Alzheimer's disease? And, if so, why? The epidemiological evidence," *Neurobiology of Aging*, vol. 22, no. 6, pp. 811–817, 2001.
- [162] P. L. McGeer and E. G. McGeer, "NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies," *Neurobiology of Aging*, vol. 28, no. 5, pp. 639–647, 2007.
- [163] C. A. Szekely, J. C. S. Breitner, A. L. Fitzpatrick et al., "NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type," *Neurology*, vol. 70, no. 1, pp. 17–24, 2008.
- [164] J. K. Boyles, L. M. Notterpek, and L. J. Anderson, "Accumulation of apolipoproteins in the regenerating and remyelinating mammalian peripheral nerve: identification of apolipoprotein D, apolipoprotein A-IV, apolipoprotein E, and apolipoprotein A-I," *Journal of Biological Chemistry*, vol. 265, no. 29, pp. 17805–17815, 1990.
- [165] J. Poirier, M. Hess, P. C. May, and C. E. Finch, "Cloning of hippocampal poly(A) RNA sequences that increase after entorhinal cortex lesion in adult rat," *Brain Research. Molecular Brain Research*, vol. 9, no. 3, pp. 191–195, 1991.

- [166] F. W. Pfrieger and B. A. Barres, "Synaptic efficacy enhanced by glial cells in vitro," *Science*, vol. 277, no. 5332, pp. 1684–1687, 1997.
- [167] D. H. Mauch, K. Nägler, S. Schumacher et al., "CNS synaptogenesis promoted by glia-derived cholesterol," *Science*, vol. 294, no. 5545, pp. 1354–1357, 2001.
- [168] I. Veinbergs, M. Mallory, M. Mante, E. Rockenstein, J. R. Gilbert, and E. Masliah, "Differential neurotrophic effects of apolipoprotein E in aged transgenic mice," *Neuroscience Letters*, vol. 265, no. 3, pp. 218–222, 1999.
- [169] D. Champagne, J. B. Dupuy, J. Rochford, and J. Poirier, "Apolipoprotein E knockout mice display procedural deficits in the Morris water maze: analysis of learning strategies in three versions of the task," *Neuroscience*, vol. 114, no. 3, pp. 641–654, 2002.
- [170] I. Gordon, E. Grauer, I. Genis, E. Sehayek, and D. M. Michaelson, "Memory deficits and cholinergic impairments in apolipoprotein E-deficient mice," *Neuroscience Letters*, vol. 199, no. 1, pp. 1–4, 1995.
- [171] H. J. Krugers, M. Mulder, J. Korf, L. Havekes, E. R. De Kloet, and M. Joëls, "Altered synaptic plasticity in hippocampal CA1 area of apolipoprotein E deficient mice," *NeuroReport*, vol. 8, no. 11, pp. 2505–2510, 1997.
- [172] P. Krzyzkowski, O. Ghribi, J. Gagné et al., "Cholinergic systems and long-term potentiation in memory-impaired apolipoprotein E-deficient mice," *Neuroscience*, vol. 92, no. 4, pp. 1273–1286, 1999.
- [173] E. Masliah, M. Mallory, I. Veinbergs, A. Miller, and W. Samuel, "Alterations in apolipoprotein E expression during aging and neurodegeneration," *Progress in Neurobiology*, vol. 50, no. 5-6, pp. 493–503, 1996.
- [174] M. S. Oitzl, M. Mulder, P. J. Lucassen, L. M. Havekes, J. Grootendorst, and E. R. De Kloet, "Severe learning deficits in apolipoprotein E-knockout mice in a water maze task," *Brain Research*, vol. 752, no. 1-2, pp. 189–196, 1997.
- [175] E. Masliah, M. Mallory, N. Ge, M. Alford, I. Veinbergs, and A. D. Roses, "Neurodegeneration in the central nervous system of apoE-deficient mice," *Experimental Neurology*, vol. 136, no. 2, pp. 107–122, 1995.
- [176] O. Kleifeld, M. F. Diebler, S. Chapman, L. Oron, and D. M. Michaelson, "The effects of apolipoprotein E deficiency on brain cholinergic neurons," *International Journal of Developmental Neuroscience*, vol. 16, no. 7-8, pp. 755–762, 1998.
- [177] D. Champagne, J. Rochford, and J. Poirier, "Effect of apolipoprotein E deficiency on reactive sprouting in the dentate gyrus of the hippocampus following entorhinal cortex lesion: role of the astroglial response," *Experimental Neurology*, vol. 194, no. 1, pp. 31–42, 2005.
- [178] I. Veinbergs and E. Masliah, "Synaptic alterations in apolipoprotein E knockout mice," *Neuroscience*, vol. 91, no. 1, pp. 401–403, 1999.
- [179] L. Lomnitski, L. Oron, D. Sklan, and D. M. Michaelson, "Distinct alterations in phospholipid metabolism in brains of apolipoprotein E-deficient mice," *Journal of Neuroscience Research*, vol. 58, no. 4, pp. 586–592, 1999.
- [180] M. Evola, A. Hall, T. Wall, A. Young, and P. Grammas, "Oxidative stress impairs learning and memory in apoE knockout mice," *Pharmacology Biochemistry and Behavior*, vol. 96, no. 2, pp. 181–186, 2010.
- [181] C. R. Jack Jr., R. C. Petersen, Y. C. Xu et al., "Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease," *Neurology*, vol. 49, no. 3, pp. 786–794, 1997.
- [182] C. Geroldi, M. Pihlajamäki, M. P. Laakso et al., "APOE-ε4 is associated with less frontal and more medial temporal lobe atrophy in AD," *Neurology*, vol. 53, no. 8, pp. 1825–1832, 1999.
- [183] R. Barber, A. Gholkar, P. Scheltens et al., "Apolipoprotein E ε4 allele, temporal lobe atrophy, and white matter lesions in late-life dementias," *Archives of Neurology*, vol. 56, no. 8, pp. 961–965, 1999.
- [184] M. Mulder, P. J. Jansen, B. J. A. Janssen et al., "Low-density lipoprotein receptor-knockout mice display impaired spatial memory associated with a decreased synaptic density in the hippocampus," *Neurobiology of Disease*, vol. 16, no. 1, pp. 212–219, 2004.
- [185] J. D. Fryer, R. B. DeMattos, L. M. McCormick et al., "The low density lipoprotein receptor regulates the level of central nervous system human and murine apolipoprotein E but does not modify amyloid plaque pathology in PDAPP mice," *Journal of Biological Chemistry*, vol. 280, no. 27, pp. 25754–25759, 2005.
- [186] C. Ramassamy, D. Averill, U. Beffert et al., "Oxidative insults are associated with apolipoprotein E genotype in Alzheimer's disease brain," *Neurobiology of Disease*, vol. 7, no. 1, pp. 23–37, 2000.
- [187] D. Cheng, R. Huang, I. S. Lanham et al., "Functional interaction between APOE4 and LDL receptor isoforms in Alzheimer's disease," *Journal of Medical Genetics*, vol. 42, no. 2, pp. 129–131, 2005.
- [188] M. Morikawa, J. D. Fryer, P. M. Sullivan et al., "Production and characterization of astrocyte-derived human apolipoprotein E isoforms from immortalized astrocytes and their interactions with amyloid-β," *Neurobiology of Disease*, vol. 19, no. 1-2, pp. 66–76, 2005.
- [189] S. Chapman, T. Sabo, A. D. Roses, and D. M. Michaelson, "Reversal of presynaptic deficits of apolipoprotein E-deficient mice in human apolipoprotein E transgenic mice," *Neuroscience*, vol. 97, no. 3, pp. 419–424, 2000.
- [190] J. Grootendorst, A. Bour, E. Vogel et al., "Human apoE targeted replacement mouse lines: H-apoE4 and h-apoE3 mice differ on spatial memory performance and avoidance behavior," *Behavioural Brain Research*, vol. 159, no. 1, pp. 1–14, 2005.
- [191] K. R. Bales, F. Liu, S. Wu et al., "Human APOE isoform-dependent effects on brain β-amyloid levels in PDAPP transgenic mice," *Journal of Neuroscience*, vol. 29, no. 21, pp. 6771–6779, 2009.
- [192] J. F. Blain, P. M. Sullivan, and J. Poirier, "A deficit in astroglial organization causes the impaired reactive sprouting in human apolipoprotein E4 targeted replacement mice," *Neurobiology of Disease*, vol. 21, no. 3, pp. 505–514, 2006.
- [193] P. M. Sullivan, B. Han, F. Liu et al., "Reduced levels of human apoE4 protein in an animal model of cognitive impairment," *Neurobiology of Aging*. In press.
- [194] B. L. Trommer, C. Shah, S. H. Yun et al., "ApoE isoform affects LTP in human targeted replacement mice," *NeuroReport*, vol. 15, no. 17, pp. 2655–2658, 2004.
- [195] D. M. Holtzman, K. R. Bales, S. Wu et al., "Expression of human apolipoprotein E reduces amyloid-β deposition in a mouse model of Alzheimer's disease," *Journal of Clinical Investigation*, vol. 103, no. 6, pp. R15–R21, 1999.
- [196] R. C. Petersen, G. E. Smith, R. J. Ivnik et al., "Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals," *Journal of the American Medical Association*, vol. 273, no. 16, pp. 1274–1278, 1995.

- [197] H. H. Feldman, S. Ferris, B. Winblad et al., "Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study," *The Lancet Neurology*, vol. 6, no. 6, pp. 501–512, 2007.
- [198] M. J. De Leon, A. Convit, O. T. Wolf et al., "Prediction of cognitive decline in normal elderly subjects with 2-[¹⁸F]fluoro-2-deoxy-D-glucose/positron-emission tomography (FDG/PET)," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 19, pp. 10966–10971, 2001.
- [199] R. J. Caselli, A. C. Dueck, D. Osborne et al., "Longitudinal modeling of age-related memory decline and the APOE $\epsilon 4$ effect," *The New England Journal of Medicine*, vol. 361, no. 3, pp. 255–263, 2009.
- [200] R. J. Caselli, E. M. Reiman, D. Osborne et al., "Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE $\epsilon 4$ allele," *Neurology*, vol. 62, no. 11, pp. 1990–1995, 2004.
- [201] L. C. Walker, J. Pahnke, M. Madauss et al., "Apolipoprotein E4 promotes the early deposition of $A\beta_{42}$ and then $A\beta_{40}$ in the elderly," *Acta Neuropathologica*, vol. 100, no. 1, pp. 36–42, 2000.
- [202] H. Jick, G. L. Zornberg, S. S. Jick, S. Seshadri, and D. A. Drachman, "Statins and the risk of dementia," *The Lancet*, vol. 356, no. 9242, pp. 1627–1631, 2000.
- [203] K. Rockwood, S. Kirkland, D. B. Hogan et al., "Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people," *Archives of Neurology*, vol. 59, no. 2, pp. 223–227, 2002.
- [204] B. Wolozin, W. Kellman, P. Ruosseau, G. G. Celesia, and G. Siegel, "Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors," *Archives of Neurology*, vol. 57, no. 10, pp. 1439–1443, 2000.
- [205] C. M. Carlsson, C. E. Gleason, T. M. Hess et al., "Effects of simvastatin on cerebrospinal fluid biomarkers and cognition in middle-aged adults at risk for Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 13, no. 2, pp. 187–197, 2008.
- [206] H. A. Wishart, A. J. Saykin, T. W. McAllister et al., "Regional brain atrophy in cognitively intact adults with a single APOE $\epsilon 4$ allele," *Neurology*, vol. 67, no. 7, pp. 1221–1224, 2006.
- [207] R. A. Honea, E. Vidoni, A. Harsha, and J. M. Burns, "Impact of APOE on the healthy aging brain: a voxel-based MRI and DTI study," *Journal of Alzheimer's Disease*, vol. 18, no. 3, pp. 553–564, 2009.
- [208] E. Canu, G. B. Frisoni, F. Agosta, M. Pievani, M. Bonetti, and M. Filippi, "Early and late onset Alzheimer's disease patients have distinct patterns of white matter damage," *Neurobiology of Aging*. In press.
- [209] H. Zhang, J. N. Trollor, W. Wen et al., "Grey matter atrophy of basal forebrain and hippocampus in mild cognitive impairment," *Journal of Neurology, Neurosurgery, and Psychiatry*. In press.
- [210] D. A. Wolk and B. C. Dickerson, "Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 22, pp. 10256–10261, 2010.
- [211] O. C. Okonkwo, M. L. Alosco, B. A. Jerskey, L. H. Sweet, B. R. Ott, and G. Tremont, "Cerebral atrophy, apolipoprotein E $\epsilon 4$, and rate of decline in everyday function among patients with amnesic mild cognitive impairment," *Alzheimer's & Dementia*, vol. 6, no. 5, pp. 404–411, 2010.
- [212] S. Kim, S. Swaminathan, L. Shen et al., "Genome-wide association study of CSF biomarkers $A\beta_{1-42}$, t-tau, and p-tau181p in the ADNI cohort," *Neurology*, vol. 76, no. 1, pp. 69–79, 2011.
- [213] M. Han, G. D. Schellenberg, and L.-S. Wang, "Genome-wide association reveals genetic effects on human $A\beta_{42}$ and τ protein levels in cerebrospinal fluids: a case control study," *BMC Neurology*, vol. 10, article 90, 2010.
- [214] L. Glodzik-Sobanska, E. Pirraglia, M. Brys et al., "The effects of normal aging and ApoE genotype on the levels of CSF biomarkers for Alzheimer's disease," *Neurobiology of Aging*, vol. 30, no. 5, pp. 672–681, 2009.
- [215] J. M. Schott, J. W. Bartlett, N. C. Fox, and J. Barnes, "Increased brain atrophy rates in cognitively normal older adults with low cerebrospinal fluid $A\beta_{1-42}$," *Annals of Neurology*, vol. 68, no. 6, pp. 825–834, 2010.
- [216] D. Tosun, N. Schuff, D. Truran-Sacrey et al., "Relations between brain tissue loss, CSF biomarkers, and the ApoE genetic profile: a longitudinal MRI study," *Neurobiology of Aging*, vol. 31, no. 8, pp. 1340–1354, 2010.
- [217] G. C. Chiang, P. S. Insel, D. Tosun et al., "Hippocampal atrophy rates and CSF biomarkers in elderly APOE2 normal subjects," *Neurology*, vol. 75, no. 22, pp. 1976–1981, 2010.
- [218] M. Thambisetty, L. Beason-Held, Y. An, M. A. Kraut, and S. M. Resnick, "APOE $\epsilon 4$ genotype and longitudinal changes in cerebral blood flow in normal aging," *Archives of Neurology*, vol. 67, no. 1, pp. 93–98, 2010.
- [219] N. Scarmeas, C. Habeck, K. E. Anderson et al., "Altered PET functional brain responses in cognitively intact elderly persons at risk for Alzheimer disease (carriers of the $\epsilon 4$ allele)," *American Journal of Geriatric Psychiatry*, vol. 12, no. 6, pp. 596–605, 2004.
- [220] I. G. McKeith, D. J. Burn, C. G. Ballard et al., "Dementia with Lewy bodies," *Seminars in Clinical Neuropsychiatry*, vol. 8, no. 1, pp. 46–57, 2003.
- [221] R. Lane, Y. He, C. Morris, J. B. Leverenz, M. Emre, and C. Ballard, "BuChE-K and APOE $\epsilon 4$ allele frequencies in lewy body dementias, and influence of genotype and hyperhomocysteinemia on cognitive decline," *Movement Disorders*, vol. 24, no. 3, pp. 392–400, 2009.
- [222] A. E. Lang, "The progression of Parkinson disease: a hypothesis," *Neurology*, vol. 68, no. 12, pp. 948–952, 2007.
- [223] A. B. Singleton, A. Wharton, K. K. O'Brien et al., "Clinical and neuropathological correlates of apolipoprotein E genotype in dementia with Lewy bodies," *Dementia and Geriatric Cognitive Disorders*, vol. 14, no. 3-4, pp. 167–175, 2002.
- [224] G. M. McKhann, M. S. Albert, M. Grossman, B. Miller, D. Dickson, and J. Q. Trojanowski, "Clinical and pathological diagnosis of frontotemporal dementia: report of the work group on Frontotemporal Dementia and Pick's Disease," *Archives of Neurology*, vol. 58, no. 11, pp. 1803–1809, 2001.
- [225] J. Kálmán, A. Juhász, K. Majtényi et al., "Apolipoprotein E polymorphism in Pick's disease and in Huntington's disease," *Neurobiology of Aging*, vol. 21, no. 4, pp. 555–558, 2000.
- [226] S. M. Pickering-Brown, F. Owen, A. Isaacs et al., "Apolipoprotein E $\epsilon 4$ allele has no effect on age at onset or duration of disease in cases of frontotemporal dementia with pick- or microvacuolar-type histology," *Experimental Neurology*, vol. 163, no. 2, pp. 452–456, 2000.
- [227] L. A. Farrer, C. R. Abraham, L. Volicer et al., "Allele $\epsilon 4$ of apolipoprotein E shows a dose effect on age at onset of Pick disease," *Experimental Neurology*, vol. 136, no. 2, pp. 162–170, 1995.

- [228] L. Gustafson, M. Abrahamson, A. Grubb, K. Nilson, and G. Fex, "Apolipoprotein-E genotyping in Alzheimer's disease and frontotemporal dementia," *Dementia and Geriatric Cognitive Disorders*, vol. 8, no. 4, pp. 240–243, 1997.
- [229] M. Hattori, Y. Hashizume, M. Yoshida et al., "Distribution of astrocytic plaques in the corticobasal degeneration brain and comparison with tuft-shaped astrocytes in the progressive supranuclear palsy brain," *Acta Neuropathologica*, vol. 106, no. 2, pp. 143–149, 2003.
- [230] J. A. Schneider, R. L. Watts, M. Gearing, R. P. Brewer, and S. S. Mirra, "Corticobasal degeneration: neuropathologic and clinical heterogeneity," *Neurology*, vol. 48, no. 4, pp. 959–969, 1997.
- [231] H. R. Morris, J. R. Vaughan, S. R. Datta et al., "Multiple system atrophy/progressive supranuclear palsy: α -synuclein, synphilin, tau, and APOE," *Neurology*, vol. 55, no. 12, pp. 1918–1920, 2000.
- [232] H. R. Morris, A. Schrag, U. Nath et al., "Effect of ApoE and tau on age of onset of progressive supranuclear palsy and multiple system atrophy," *Neuroscience Letters*, vol. 312, no. 2, pp. 118–120, 2001.
- [233] Y. Baba, J. D. Putzke, Y. Tsuboi et al., "Effect of MAPT and APOE on prognosis of progressive supranuclear palsy," *Neuroscience Letters*, vol. 405, no. 1-2, pp. 116–119, 2006.
- [234] A. Anouti, K. Schmidt, K. E. Lyons et al., "Normal distribution of apolipoprotein E alleles in progressive supranuclear palsy," *Neurology*, vol. 46, no. 4, pp. 1156–1157, 1996.
- [235] M. Tabaton, M. Rolleri, P. Masturzo et al., "Apolipoprotein E ϵ 4 allele frequency is not increased in progressive supranuclear palsy," *Neurology*, vol. 45, no. 9, pp. 1764–1765, 1995.
- [236] A. Sawa, N. Amano, N. Yamada et al., "Apolipoprotein E in progressive supranuclear palsy in Japan," *Molecular Psychiatry*, vol. 2, no. 4, pp. 341–342, 1997.
- [237] D. Aarsland, J. Zaccai, and C. Brayne, "A systematic review of prevalence studies of dementia in Parkinson's disease," *Movement Disorders*, vol. 20, no. 10, pp. 1255–1263, 2005.
- [238] D. Aarsland and M. W. Kurz, "The epidemiology of dementia associated with Parkinson disease," *Journal of the Neurological Sciences*, vol. 289, no. 1-2, pp. 18–22, 2010.
- [239] J. E. Galvin, J. Pollack, and J. C. Morris, "Clinical phenotype of Parkinson disease dementia," *Neurology*, vol. 67, no. 9, pp. 1605–1611, 2006.
- [240] M. N. Sabbagh, C. H. Adler, T. J. Lahti et al., "Parkinson disease with dementia: comparing patients with and without Alzheimer pathology," *Alzheimer Disease and Associated Disorders*, vol. 23, no. 3, pp. 295–297, 2009.
- [241] D. C. Rubinsztein, C. S. Hanlon, R. M. Irving et al., "Apo E genotypes in multiple sclerosis, Parkinson's disease, schwannomas and late-onset Alzheimer's disease," *Molecular and Cellular Probes*, vol. 8, no. 6, pp. 519–525, 1994.
- [242] W. C. Koller, S. L. Glatt, J. P. Hubble et al., "Apolipoprotein E genotypes in Parkinson's disease with and without dementia," *Annals of Neurology*, vol. 37, no. 2, pp. 242–245, 1995.
- [243] D. Ibarreta, T. Gómez-Isla, A. Portera-Sánchez, R. Parrilla, and M. S. Ayuso, "Apolipoprotein E genotype in Spanish patients of Alzheimer's or Parkinson's disease," *Journal of the Neurological Sciences*, vol. 134, no. 1-2, pp. 146–149, 1995.
- [244] C. M. Morris, H. M. Massey, R. Benjamin et al., "Molecular biology of APO E alleles in Alzheimer's and non-Alzheimer's dementias," *Journal of Neural Transmission, Supplementum*, no. 47, pp. 205–218, 1996.
- [245] A. S. Whitehead, S. Bertrand, F. Finnan, A. Butler, G. D. Smith, and Y. Ben-Shlomo, "Frequency of the apolipoprotein E ϵ 4 allele in a case-control study of early onset Parkinson's disease," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 61, no. 4, pp. 347–351, 1996.
- [246] D. St Clair, "Apolipoprotein E gene in Parkinson's disease, Lewy body dementia and Alzheimer's disease," *Journal of Neural Transmission, Supplementum*, no. 51, pp. 161–165, 1997.
- [247] J. Eerola, J. Launes, O. Hellström, and P. J. Tienari, "Apolipoprotein E (APOE), PARKIN and catechol-O-methyltransferase (COMT) genes and susceptibility to sporadic Parkinson's disease in Finland," *Neuroscience Letters*, vol. 330, no. 3, pp. 296–298, 2002.
- [248] H. Vefring, K. Haugarvoll, O.-B. Tysnes, J. P. Larsen, and M. W. Kurz, "The role of APOE alleles in incident Parkinson's disease. The Norwegian ParkWest Study," *Acta Neurologica Scandinavica*, vol. 122, no. 6, pp. 438–441, 2010.
- [249] L. Blázquez, D. Otaegui, A. Sáenz et al., "Apolipoprotein E ϵ 4 allele in familial and sporadic Parkinson's disease," *Neuroscience Letters*, vol. 406, no. 3, pp. 235–239, 2006.
- [250] A. Parsian, B. Racette, L. J. Goldsmith, and J. S. Perlmutter, "Parkinson's disease and apolipoprotein E: possible association with dementia but not age at onset," *Genomics*, vol. 79, no. 3, pp. 458–461, 2002.
- [251] N. Pankratz, L. Byder, C. Halter et al., "Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia," *Movement Disorders*, vol. 21, no. 1, pp. 45–49, 2006.
- [252] A. I. Tröster, J. A. Fields, A. M. Paolo, and W. C. Koller, "Absence of the apolipoprotein E ϵ 4 allele is associated with working memory impairment in Parkinson's disease," *Journal of the Neurological Sciences*, vol. 248, no. 1-2, pp. 62–67, 2006.
- [253] S. Papapetropoulos, M. J. Farrer, J. T. Stone et al., "Phenotypic associations of tau and ApoE in Parkinson's disease," *Neuroscience Letters*, vol. 414, no. 2, pp. 141–144, 2007.
- [254] B. S. Harhangi, M. C. De Rijk, C. M. van Duijn, C. van Broeckhoven, A. Hofman, and M. M. B. Breteler, "APOE and the risk of PD with or without dementia in a population-based study," *Neurology*, vol. 54, no. 6, pp. 1272–1276, 2000.
- [255] Y. J. Li, M. A. Hauser, W. K. Scott et al., "Apolipoprotein E controls the risk and age at onset of Parkinson disease," *Neurology*, vol. 62, no. 11, pp. 2005–2009, 2004.
- [256] S. Zarepari, J. Kaye, R. Camicioli et al., "Modulation of the age at onset of Parkinson's disease by apolipoprotein E genotypes," *Annals of Neurology*, vol. 42, no. 4, pp. 655–658, 1997.
- [257] D. D. Buchanan, P. A. Silburn, J. A. Prince, and G. D. Mellick, "Association of APOE with Parkinson disease age-at-onset in women," *Neuroscience Letters*, vol. 411, no. 3, pp. 185–188, 2007.
- [258] X. Huang, P. C. Chen, and C. Poole, "APOE- ϵ 2 allele associated with higher prevalence of sporadic Parkinson disease," *Neurology*, vol. 62, no. 12, pp. 2198–2202, 2004.
- [259] G. Tang, H. Xie, L. Xu, Y. Hao, D. Lin, and D. Ren, "Genetic study of apolipoprotein E gene, alpha-1 antichymotrypsin gene in sporadic Parkinson disease," *American Journal of Medical Genetics*, vol. 114, no. 4, pp. 446–449, 2002.
- [260] X. Huang, P. Chen, D. I. Kaufer, A. I. Tröster, and C. Poole, "Apolipoprotein E and dementia in Parkinson disease: a meta-analysis," *Archives of Neurology*, vol. 63, no. 2, pp. 189–193, 2006.

- [261] M. Noutsias, M. Rohde, A. Block et al., "Pre-amplification techniques for real-time RT-PCR analyses of endomyocardial biopsies," *BMC Molecular Biology*, vol. 9, article 3, 2008.
- [262] M. Panas, D. Avramopoulos, G. Karadima, M. B. Petersen, and D. Vassilopoulos, "Apolipoprotein E and presenilin-1 genotypes in Huntington's disease," *Journal of Neurology*, vol. 246, no. 7, pp. 574–577, 1999.
- [263] P. Kehoe, M. Krawczak, P. S. Harper, M. J. Owen, and A. L. Jones, "Age of onset in Huntington disease: sex specific influence of apolipoprotein E genotype and normal CAG repeat length," *Journal of Medical Genetics*, vol. 36, no. 2, pp. 108–111, 1999.
- [264] C. Saft, J. E. Andrich, N. Brune et al., "Apolipoprotein E genotypes do not influence the age of onset in Huntington's disease," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 75, no. 12, pp. 1692–1696, 2004.
- [265] R. M. Burwick, P. P. Ramsay, J. L. Haines et al., "APOE epsilon variation in multiple sclerosis susceptibility and disease severity: some answers," *Neurology*, vol. 66, no. 9, pp. 1373–1383, 2006.
- [266] N. J. Cairns, P. F. Atkinson, T. Kovács, A. J. Lees, S. E. Daniel, and P. L. Lantos, "Apolipoprotein E e4 allele frequency in patients with multiple system atrophy," *Neuroscience Letters*, vol. 221, no. 2-3, pp. 161–164, 1997.
- [267] J. Phukan, N. P. Pender, and O. Hardiman, "Cognitive impairment in amyotrophic lateral sclerosis," *The Lancet Neurology*, vol. 6, no. 11, pp. 994–1003, 2007.
- [268] V. E. Drory, M. Birnbaum, A. D. Korczyn, and J. Chapman, "Association of APOE $\epsilon 4$ allele with survival in amyotrophic lateral sclerosis," *Journal of the Neurological Sciences*, vol. 190, no. 1-2, pp. 17–20, 2001.
- [269] S. Schmidt, L. C. Kwee, K. D. Allen, and E. Z. Oddone, "Association of ALS with head injury, cigarette smoking and APOE genotypes," *Journal of the Neurological Sciences*, vol. 291, no. 1-2, pp. 22–29, 2010.
- [270] B. Moulard, A. Sefiani, A. Laamri, A. Malafosse, and W. Camu, "Apolipoprotein E genotyping in sporadic amyotrophic lateral sclerosis, evidence for a major influence on the clinical presentation and prognosis," *Journal of the Neurological Sciences*, vol. 139, pp. 34–37, 1996.
- [271] S. Mui, G. W. Rebeck, D. McKenna-Yasek, B. T. Hyman, and R. H. Brown, "Apolipoprotein E $\epsilon 4$ allele is not associated with earlier age at onset in amyotrophic lateral sclerosis," *Annals of Neurology*, vol. 38, no. 3, pp. 460–463, 1995.
- [272] H. Zetterberg, J. Jacobsson, L. Rosengren, K. Blennow, and P. M. Andersen, "Association of APOE with age at onset of sporadic amyotrophic lateral sclerosis," *Journal of the Neurological Sciences*, vol. 273, no. 1-2, pp. 67–69, 2008.
- [273] Y. J. Li, M. A. Pericak-Vance, J. L. Haines et al., "Apolipoprotein E is associated with age at onset of amyotrophic lateral sclerosis," *Neurogenetics*, vol. 5, no. 4, pp. 209–213, 2004.
- [274] L. Lacomblez, V. Doppler, I. Beucler et al., "APOE: a potential marker of disease progression in ALS," *Neurology*, vol. 58, no. 7, pp. 1112–1114, 2002.
- [275] F. Fazekas, S. Strasser-Fuchs, H. Kollegger et al., "Apolipoprotein E $\epsilon 4$ is associated with rapid progression of multiple sclerosis," *Neurology*, vol. 57, no. 5, pp. 853–857, 2001.
- [276] S. Schmidt, L. F. Barcellos, K. DeSombre et al., "Association of polymorphisms in the apolipoprotein E region with susceptibility to and progression of multiple sclerosis," *American Journal of Human Genetics*, vol. 70, no. 3, pp. 708–717, 2002.
- [277] J. Chapman, S. Vinokurov, A. Achiron et al., "APOE genotype is a major predictor of long-term progression of disability in MS," *Neurology*, vol. 56, no. 3, pp. 312–316, 2001.
- [278] M. Pinholt, J. L. Frederiksen, P. S. Andersen, and M. Christiansen, "Apo E in multiple sclerosis and optic neuritis: the Apo E- $\epsilon 4$ allele is associated with progression of multiple sclerosis," *Multiple Sclerosis*, vol. 11, no. 5, pp. 511–515, 2005.
- [279] M. Pinholt, J. L. Frederiksen, and M. Christiansen, "The association between apolipoprotein E and multiple sclerosis," *European Journal of Neurology*, vol. 13, no. 6, pp. 573–580, 2006.
- [280] P. Høgh, A. Oturai, K. Schreiber et al., "Apolipoprotein E and multiple sclerosis: impact of the epsilon-4 allele on susceptibility, clinical type and progression rate," *Multiple Sclerosis*, vol. 6, no. 4, pp. 226–230, 2000.
- [281] S. J. M. Weatherby, C. L. A. Mann, M. B. Davies et al., "Polymorphisms of apolipoprotein E; outcome and susceptibility in multiple sclerosis," *Multiple Sclerosis*, vol. 6, no. 1, pp. 32–36, 2000.
- [282] J. Chapman, A. D. Korczyn, D. M. Karussis, and D. M. Michaelson, "The effects of APOE genotype on age at onset and progression of neurodegenerative diseases," *Neurology*, vol. 57, no. 8, pp. 1482–1485, 2001.
- [283] O. H. Kantarci, D. D. Hebrink, S. J. Achenbach et al., "Association of APOE polymorphisms with disease severity in MS is limited to women," *Neurology*, vol. 62, no. 5, pp. 811–814, 2004.
- [284] J. Zwemmer, B. Uitdehaag, G. van Kamp, F. Barkhof, C. Polman, and B. G. Weinshenker, "Association of APOE polymorphisms with disease severity in MS is limited to women," *Neurology*, vol. 63, no. 6, p. 1139, 2004.
- [285] C. M. Bojanowski, D. Shen, E. Y. Chew et al., "An apolipoprotein E variant may protect against age-related macular degeneration through cytokine regulation," *Environmental and Molecular Mutagenesis*, vol. 47, no. 8, pp. 594–602, 2006.
- [286] A. Thakkinian, S. Bowe, M. McEvoy, W. Smith, and J. Attia, "Association between apolipoprotein E polymorphisms and age-related macular degeneration: a HuGE review and meta-analysis," *American Journal of Epidemiology*, vol. 164, no. 9, pp. 813–822, 2006.
- [287] K. A. Kovács, Z. Pámer, A. Kovács et al., "Association of apolipoprotein E polymorphism with age-related macular degeneration and Alzheimer's disease in south-western Hungary," *Ideggyógyászati Szemle*, vol. 60, no. 3-4, pp. 169–172, 2007.
- [288] P. N. Baird, E. Guida, D. T. Chu, H. T. V. Vu, and R. H. Guymer, "The $\epsilon 2$ and $\epsilon 4$ alleles of the apolipoprotein gene are associated with age-related macular degeneration," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 5, pp. 1311–1315, 2004.
- [289] G. Malek, L. V. Johnson, B. E. Mace et al., "Apolipoprotein E allele-dependent pathogenesis: a model for age-related retinal degeneration," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 33, pp. 11900–11905, 2005.
- [290] R. Aleong, N. Aumont, D. Dea, and J. Poirier, "Non-steroidal anti-inflammatory drugs mediate increased in vitro glial expression of apolipoprotein E protein," *European Journal of Neuroscience*, vol. 18, no. 6, pp. 1428–1438, 2003.
- [291] J. Poirier, "Apolipoprotein E represents a potent gene-based therapeutic target for the treatment of sporadic Alzheimer's disease," *Alzheimer's and Dementia*, vol. 4, no. 1, supplement 1, pp. S91–S97, 2008.

- [292] M. E. Risner, A. M. Saunders, J. F. B. Altman et al., "Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease," *Pharmacogenomics Journal*, vol. 6, no. 4, pp. 246–254, 2006.
- [293] J. Rogers, L. C. Kirby, S. R. Hempelman et al., "Clinical trial of indomethacin in Alzheimer's disease," *Neurology*, vol. 43, no. 8, pp. 1609–1611, 1993.
- [294] D. J. Stone, I. Rozovsky, T. E. Morgan, C. P. Anderson, and C. E. Finch, "Increased synaptic sprouting in response to estrogen via an apolipoprotein E-dependent mechanism: implications for Alzheimer's disease," *Journal of Neuroscience*, vol. 18, no. 9, pp. 3180–3185, 1998.