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Lipids and Lipoproteins in Alzheimer's Disease

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1. Introduction

Cholesterol is a key structural component of the brain, and cholesterol transport and distribution within the central nervous system (CNS) is mediated by a lipid metabolic cycle that includes generation of apolipoproteins as lipid carriers, lipidation by cholesterol and phospholipid transporters, enzyme remodeling of these particles and their receptor-mediated uptake and turnover in cells. It is becoming increasingly appreciated that Alzheimer's Disease (AD) patients often have comorbid conditions such as cardiovascular disease, type II diabetes mellitus, or hypertension, each of which can greatly affect lipoprotein metabolism, especially at the vessel wall and thereby possibly contribute to AD pathogenesis. Here we review the known biology of lipids and lipoproteins in the CNS and discuss how alterations in lipid metabolism may impact AD pathogenesis. Apolipoprotein E (*APOE*) is the best established genetic risk factor for AD and the major apolipoprotein expressed in the brain. In addition, genome-wide association studies (GWAS) have identified several other genes associated with AD risk that function in lipid or lipoprotein metabolism, including clusterin (*CLU*), ATP binding cassette (ABC) transporter A7 (*ABCA7*), and apoE receptors. Understanding how lipid/lipoprotein metabolism in the brain and body affect cognitive function may therefore offer new insights in developing more effective therapeutic approaches for dementia.

2. Lipid and lipoprotein metabolism in the CNS

2.1. General biology and function of lipids and lipoproteins in the CNS

The brain is the most cholesterol-rich organ in the body, with an average cholesterol content of 15-20 mg/g wet weight compared to 2 mg/g for peripheral tissues in the adult mouse [1].

The majority of the brain’s sterol content is located in free cholesterol, 70-80% of which is in myelin. Cholesterol, sphingomyelin and phospholipids form the major structural components of cellular membranes, with cholesterol, phosphatidylcholine and phosphatidylethanolamine being the most abundant lipids in synaptic vesicles [2]. Many lipids also participate in important signaling pathways in the brain, with lipid-mediated second messengers derived from sphingomyelin and phosphatidylinositol, activation of G- protein coupled receptors and nuclear receptor activation being particularly important [1, 3].

Name	Major Sites of Production in the Brain	Main Functions in Healthy Brain	Potential Role in AD
ApoE	<ul style="list-style-type: none">• Astrocytes• Microglia	<ul style="list-style-type: none">• Lipid transport• Aβ homeostasis• BBB integrity• Cerebrovascular health• Innate immune response• Reelin signaling	<ul style="list-style-type: none">• Involved in Aβ metabolism: deposition, transport across the BBB, clearance through ISF and the CSF pathways, and enzymatic degradation• Regulation of inflammation• ApoE4, the most established AD genetic risk factor, is associated with:<ul style="list-style-type: none">1. Impaired Aβ degradation and clearance2. Increased tau phosphorylation and formation of NFT3. Ineffective lipid transport4. Impaired synaptic integrity5. Reduced ability to suppress inflammation
Clusterin	<ul style="list-style-type: none">• Astrocytes• Choroid plexus epithelial cells• Neurons	<ul style="list-style-type: none">• Golgi chaperone• Inflammatory response• Complement regulation• Cell Cycle regulation• Reelin signaling	<ul style="list-style-type: none">• Third most highly associated susceptibility locus for AD.• Potentially involved in Aβ sequestration, degradation and clearance
ApoA-I	<ul style="list-style-type: none">• Not produced in the brain	<ul style="list-style-type: none">• Reverse cholesterol transport• Vascular endothelial health	<ul style="list-style-type: none">• AD comorbidities such as type II diabetes and hypercholesterolemia lead to apoA-I dysfunction• Reduction of CAA, neuroinflammation, and oxidative stress in mouse models of AD

Table 1. Major Apolipoproteins in the Brain

As lipids are insoluble in aqueous environments, neutral lipids are transported through bodily fluids on lipoprotein particles consisting of amphipathic apolipoproteins that surround and stabilize their lipid cargo. The general structure of mature spherical lipoproteins consists of a core of neutral cholesterol ester and triglycerides surrounded by amphipathic free cholesterol and phospholipids at the exposed surface, all of which are encapsulated by apolipoproteins

[3]. Four major lipoprotein classes, defined by their buoyant density, are found in the circulation: high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons. While LDL, VLDL and chylomicrons are triglyceride rich, HDL is triglyceride poor, and the HDL-like lipoprotein species found within the CNS contain even less triglyceride than plasma HDL. As apolipoprotein B (apoB), the major apolipoprotein of chylomicrons, VLDL, and LDL, is not found in the CNS, lipoprotein metabolism in the brain and cerebrospinal fluid (CSF) is based entirely on a lipoprotein class that most resembles plasma HDL with respect to size, shape, and density [4-11]. In rodents, astrocytes secrete apoE-containing lipoproteins that are primarily composed of phospholipids (~6 µg/ml) and cholesterol (~13 µg/ml), 0-18% of which is found in the esterified form. These nascent lipoprotein particles are discoidal, ranging from 9-17 nm in diameter with a density of 1.00-1.12 g/ml [7, 10]. Clusterin, also known as apolipoprotein J (apoJ), is also produced by astrocytes but is secreted virtually free of lipids [7, 10, 12]. Conversely, whereas lipoprotein particles found in CSF are of a similar diameter (11-20 nm) and density (1.063-1.12 g/ml) to those secreted by astrocytes, they are distinguished by their spherical shape and a greater proportion of phospholipids and cholesterol, with approximately 70% of cholesterol found as cholesterol esters [5, 7, 8, 10, 13]. ApoE and apolipoprotein A-I (apoA-I) are the major apolipoproteins present in CSF by mass, with apolipoproteins A-II, A-IV, D, CI, CIII, and clusterin also present to a lesser extent [5, 8-11]. In the healthy CNS, lipoproteins regulate the transport, delivery and distribution of lipids. In addition, lipoproteins are also thought to regulate many functions in the CNS including inflammation, oxidative stress, vascular tone, cerebral blood flow, and blood brain barrier (BBB) integrity (Table 1) [14].

2.2. Apolipoproteins present in the CNS

ApoE is present at 2-10 µg/ml in human and mouse CSF [8, 13, 15, 16] and at 10-50 ng/ml in interstitial fluid (ISF) from both wild-type mice as well as in targeted replacement mice that express human apoE [17]. ApoE is the most abundant apolipoprotein expressed within the brain, where it is synthesized and secreted by astrocytes and, to a lesser extent, microglia [5]. Secreted apoE particles are lipid-rich, containing equal amounts of apoE and lipid, and carry cholesterol secreted by astrocytes [10, 18]. Indeed, lipidation of apoE is essential for its stability and function [19-21]. Humans express three *APOE* isoforms that differ from one another by two amino acid residues; *APOE2* (cys112, cys158), *APOE3* (cys112, arg158) and *APOE4* (arg112, arg158), with the *APOE3* allele being the most common and the *APOE2* allele being the least frequent in the general population [19]. The resulting apoE2, apoE3 and apoE4 proteins therefore have both structural differences with respect to protein folding as well as functional interactions with respect to their ability to bind to lipids and apoE receptors [22]. In addition to mediating cholesterol transport to neurons, apoE has other functions in the brain such as regulating vascular health and the innate immune system (Table 1) [23].

Brain tissue has one of the highest concentrations of clusterin, which is expressed in astrocytes, epithelial cells of the choroid plexus, and selected neuronal subsets [24]. As a result, clusterin is present in CSF at concentrations of 4-6.5 µg/ml in healthy human adults [25]. In humans, due to the presence of three alternative mRNA start sites, the clusterin gene *CLU* is expressed

as three transcriptional isoforms. At the protein level, clusterin exists in two major forms: a 50 kDa nuclear form and a 75-80 kDa glycosylated secreted form [26]. Although clusterin is best known for its role as a chaperone, it also appears to be involved in the inflammatory response and complement regulation, the cell cycle, and endocrine functions (Table 1) [27].

Unlike apoE and clusterin, apoA-I is not expressed in either murine or human brain [28-31], suggesting that its presence in the CNS reflects transport across the BBB and/or the blood-CSF-barrier (BCSFB) following its production from hepatocytes and enterocytes. Although *in vitro* experiments suggest that apoA-I can transcytose across cultured endothelial cells [32], an *in vivo* study shows that peripherally injected apoA-I rapidly localizes to choroid plexus epithelial cells with negligible association in cerebrovascular endothelial cells, suggesting that peripherally derived apoA-I may gain access to the CNS primarily by crossing the BCSFB [31]. The concentration of apoA-I in CSF is ~3-4 µg/mL, or 0.26% of plasma levels, in humans [8, 13, 15, 33] and 0.02 µg/mL, or 0.01% of plasma levels, in wild-type mice [31]. The physiological functions of apoA-I in the CNS are not well understood but are hypothesized to be similar to those of CNS apoE (Table 1) [14].

In addition to apoE, clusterin, and apoA-I, other apolipoproteins are also detected in the CNS, including apoD, apoC-I, apoC-III, apoA-II, and apoA-IV [8, 9, 11], each of which is detected in human CSF [5, 8-11]. It has been shown that apoD, an apolipoprotein with antioxidant and anti-inflammatory properties, is produced in neuroglial cells, pia mater cells, and perivascular cells in the human brain [34, 35].

2.3. Cholesterol and Phospholipid Transporters

Lipid-poor apolipoproteins receive cholesterol and phospholipids from membrane bound transporters that are part of the ABC transporter family. The ubiquitously expressed transporter ABCA1 mediates the transfer of cellular cholesterol and phospholipids from cellular membranes to lipid-poor apolipoprotein acceptors including apoA-I and apoE [36- 39], a process that is essential for the production of both plasma and CSF HDL. HDL plays a critical role in the regulation of lipid homeostasis, and is particularly important for cells such as macrophages and microglia that form part of the innate immune system. ABCA1 activity in these phagocytic cells is exquisitely sensitive to cholesterol accumulation, and by catalyzing efflux of excess cholesterol and phospholipids to apoA-I and apoE acceptors, ABCA1 activity helps to maintain intracellular cholesterol balance. In humans, mutations that block ABCA1 function cause Tangier Disease, which is characterized by a 95% loss of plasma HDL cholesterol and apoA-I levels due to rapid catabolism of lipid-poor apoA-I by the kidney. ABCA1-dependent lipidation of CNS apoE is also critical for its stability as both total body and brain-specific loss of ABCA1 in mice leads to a significant 60-80% reduction of brain and CSF apoE [20, 21, 30]. Whether ABCA1 also regulates apoE levels in the brain of Tangier Disease patients is not known. Notably, Wahrle et al. did not observe significant differences in CSF apoE levels between control subjects versus those with ten different *ABCA1* single nucleotide polymorphisms (SNPs), suggesting that these SNPs may not have a significant effect on human ABCA1 function in the CNS [16]. In mice, total body deletion of ABCA1 results in a significant and proportional reduction of apoA-I levels by 60-90% in plasma, brain tissue and CSF [40].

Intriguingly, brain-specific deletion of ABCA1 in mice leads to a significant increase of apoA-I protein levels in brain tissue and CSF [30]. The mechanisms that regulate the distribution of apoA-I between peripheral and CNS compartments remain to be fully determined.

Highly homologous to ABCA1, ABCA7 is also abundantly expressed in microglia, oligodendrocytes, neurons, and astrocytes in both humans [41] and mice [42, 43]. Although the potential for ABCA7 to act as a cholesterol and/or phospholipid transporter in the CNS is unknown, when overexpressed in human embryonic kidney cells, ABCA7 can mediate the transfer of phospholipids and sphingomyelin, but not cholesterol, to lipid-poor apoA-I and apoE [42]. The relative contribution of ABCA7 to the *in vivo* generation of plasma HDL cholesterol appears to be minimal and may be influenced by sex, as decreases in plasma total cholesterol and HDL cholesterol are only detected in female *Abca7*^{-/-} mice [43]. Instead, ABCA7 may be more involved in modulating the phagocytic activity of macrophages, particularly following injury or infection; whether this is also true in brain microglia will be important to address in the future [44, 45]. One critical difference between ABCA1 and ABCA7 is the distinct manner in which they are regulated by cholesterol. Whereas ABCA1 expression is induced by activation of the Liver-X-Receptor (LXR) pathway in response to increased cellular cholesterol content, ABCA7 induction is unaffected [42, 43]. Instead, ABCA7 expression is primarily regulated by sterol regulatory element binding protein 2 (SREBP-2) and is thus repressed in cholesterol-laden cells [44].

Following initial lipidation, nascent HDL lipoproteins can receive additional lipids from the cholesterol transporters ABCG1 and ABCG4 [46], which are abundantly expressed in grey and white matter of the brain [47]. Unlike ABCG4, whose expression appears to be restricted to neurons, astrocytes, and the retina, ABCG1 is widely expressed throughout the body and is found in the liver, intestine, lungs, kidney and spleen in addition to neurons, astrocytes, microglia, and choroid plexus epithelial cells [47, 48]. In addition to lipid efflux activity, ABCG1 and ABCG4 are also believed to regulate intracellular transport of cholesterol and sterols and vesicle trafficking in the brain [47, 48].

2.4. Enzymes involved in lipoprotein metabolism

Many enzymes involved in lipoprotein metabolism are found in CSF, although for most, their CNS expression patterns and functional roles have not been explored to the same extent as in the periphery. For example, lecithin cholesterol acyltransferase (LCAT), phospholipid transfer protein (PLTP), and cholesteryl ester transfer protein (CETP) are all detectable in brain tissue and CSF [13, 49-53] and, as they have established roles in plasma lipoprotein metabolism, it is of interest to understand whether they function similarly in the brain.

In plasma, LCAT is the enzyme responsible for generating the cholesterol ester core characteristic of mature circulating lipoproteins, including HDL. As the more hydrophobic cholesterol esters migrate to the core of the lipoprotein particle, the discoidal nascent particle takes on its mature spherical shape. LCAT-mediated esterification of cholesterol serves not only to generate mature HDL particles, but also to maintain the downward cholesterol gradient between the cell and the lipoprotein particle, enabling further cholesterol efflux [54]. LCAT is present in human CSF at levels corresponding to 2.2-2.5% of that in serum and migrates with

γ -like lipoproteins [13, 49]. In mice, LCAT is secreted mainly by astrocytes, can be activated by both apoA-I and apoE, and esterifies free cholesterol contained on glial-derived apoE-containing lipoproteins [55]. LCAT may therefore play a role in maturation of discoidal lipoprotein particles secreted from glia to the spherical particles that circulate in CSF by catalyzing the cholesterol esterification of immature CNS lipoprotein particles [5, 7, 56].

PLTP is another enzyme intimately involved in the maturation and turnover of lipoprotein particles within the circulation and CNS. PLTP's primary activity involves the transfer of phospholipids between HDL particles, thus modulating HDL size and composition, and transferring lipids between apoB-containing lipoprotein particles and HDL [53]. Within the CNS, PLTP is highly expressed by neurons, astrocytes, microglia, oligodendrocytes, BBB endothelial cells, choroid plexus ependymal cells and can be found both in brain tissue and CSF in human and animals [57-61]. Within CSF, PLTP is associated with apoE-containing lipoproteins where it actively participates in phospholipid transport [13, 62, 63] with activity corresponding to 15% of plasma levels in humans [62] and 23% of plasma levels in rabbits [59]. Functionally, PLTP has been reported to regulate apoE expression and secretion by astrocytes [63] and participate in neuronal cell signalling [64].

In plasma, CETP catalyses the bi-directional transfer of cholesterol esters from HDL in exchange for triglycerides from VLDL and LDL, thereby reducing circulating HDL concentration and increasing its size [65]. CETP can potentially diffuse through the BCSFB and enter the brain from plasma. However, it is not clear whether CETP is produced in the brain. Yamada et al. reported CETP-like immunoreactivity in astrocytes in healthy human brain [51]. Albers et al. have suggested that CETP is locally produced in the brain, as they were able to detect CETP in human CSF samples at concentrations higher than what would be expected from simple diffusion of proteins across the BCSFB [66]. However, Demeester et al. were unable to detect CETP in human CSF and CETP mRNA in the human brain [13]. A few other studies have also not detected CETP mRNA in the CNS of rabbits and cynomolgus monkeys [59, 67]. Undoubtedly, more research on the production and the role of CETP in the CNS of healthy individuals is needed.

2.5. Receptors involved in lipoprotein uptake and turnover

Lipoprotein uptake and delivery of lipids into target cells of the CNS is regulated by the low density lipoprotein receptor (LDLR) family [68]. The four major apoE receptors in the CNS are LDLR, lipoprotein receptor related protein-1 (LRP1), very low density lipoprotein receptor (VLDLR), and apolipoprotein E receptor 2 (apoER2) [69]. Of these, LDLR is the only receptor that has apoE as its only known ligand in the CNS [69]. LDLR and LRP1 levels are inversely correlated with brain apoE levels as deletion or overexpression of these receptors in mice increases or decreases brain apoE levels, respectively [70-73]. VLDLR and apoER2 also serve as essential receptors for the neuromodulatory ligand Reelin, which is involved in long term potentiation, learning and memory [74-76]. Like apoE, clusterin can also bind to VLDLR and apoER2 to regulate Reelin signaling (Table 1) [77]. LDLR, LRP1, VLDLR and apoER2 are all expressed on neurons, which have a high LRP1:LDLR ratio. LRP1 and LDLR are also found on astrocytes, which have a low LRP1:LDLR ratio, and LRP1 and VLDLR are found on

microglia [78-81]. Solubilized forms of these receptors, generated via ectodomain shedding or splice variants lacking the transmembrane domain, possibly contribute to negative feedback and inhibition of lipoprotein uptake [82]. Of note, the lipoprotein related protein 2 (LRP2), also known as megalin, and the neuronal sortilin- related receptor (SORL1 receptor) are also additional apoE receptors expressed in the CNS [83, 84].

3. Alterations to lipids and lipoproteins in Alzheimer's disease

The neuropathology of AD is defined by the presence of amyloid plaques and neurofibrillary tangles (NTFs), which are composed of deposited amyloid-beta ($A\beta$) peptides and filamentous hyperphosphorylated tau, respectively [85]. In addition to parenchymal amyloid plaques, most AD patients also have accumulation of amyloid in cerebral blood vessels, known as cerebral amyloid angiopathy (CAA) [14, 86]. Furthermore, neuronal degeneration and dysfunction, the brains of AD patients are often marked by significant signs of chronic inflammation, oxidative stress and vascular dysfunction. Not surprisingly, apolipoproteins, the lipids they carry, and the transporters responsible for their lipidation may be intimately involved in each step of the disease. In particular, the interrelationship between cerebrovascular dysfunction and AD is increasingly appreciated. Epidemiological, clinical, neuropathological and pathophysiological evidence shows that several cardiovascular risk factors also increase AD risk, including age, sex, hypertension, dyslipidemia, and type II diabetes [87-90]. Dementia progresses more rapidly in patients with cerebral infarcts [90- 93] and infarction and other forms of brain injury may potentiate AD pathophysiology [94- 96]. Importantly, many of these cardiovascular risk factors include aspects of dysfunctional lipid and lipoprotein metabolism, which likely occurs at the vessel wall. However, compared to the wealth of knowledge about lipid and lipoprotein physiology in large peripheral vessels, little is known about the mechanisms by which vascular risk factors for AD may impair the function of cerebral vessels. Importantly, BBB dysfunction may contribute to inflammatory processes in the CNS, where exacerbated inflammatory responses or failure to resolve inflammatory reactions are increasingly recognized to play important roles in AD pathogenesis [97].

3.1. Changes in brain lipid composition and their direct effects in AD

One often overlooked neuropathological observation initially reported by Alois Alzheimer is the presence of adipose inclusions in the brain, which Alzheimer defined as “extraordinarily strong accumulation of lipoid material in the ganglion cells, glia and vascular wall cells, and the particularly numerous fibril-forming glia cells in the cortex and, indeed, in the entire central nervous system” [98]. Almost all major classes of lipids have some correlation with AD pathogenesis [99]. A recent review by Kosicek and Hecimovic reported that the *post-mortem* brain levels of phosphatidylinositol, phosphatidylethanolamine, ethanolamine plasmalogen, and sulfatide are decreased in AD, while the levels of ceramide are increased [100]. Though not as extensively studied, it has been reported that CSF levels of ceramide are increased, while the levels of sulfatide are decreased in AD [101, 102]. Furthermore, studies by Soderberg et al. and Tully et al. report lower levels of n-3 and n-6 polyunsaturated fatty acids, which are major

components of phospholipids, in AD brain compared to healthy controls [103, 104]. Changes to the levels of these lipid classes affects not only the structural properties of the membranes, but also numerous signaling and trafficking pathways that are heavily involved in the normal functioning of the cells in the CNS [99, 105].

Changes to CNS lipid composition can also influence the production of A β peptides. As the generation of these peptides involves several lipid-associated steps, including intracellular trafficking and inter-membrane proteolytic cleavage, it is not surprising that, in addition to genetic changes that alter A β production, there are also indirect, lipid-dependent changes that can affect production of A β . A β peptides are derived via sequential proteolytic processing of the amyloid precursor protein (APP) by β -secretase and γ -secretase. This leads to liberation of A β peptides 38-46 amino acids in length into the extracellular space [106-108]. Of these, A β 40 and A β 42 are quantitatively the most important for amyloid deposition [109]. In healthy brains, the vast majority of APP is processed by α -secretase, followed by γ -secretase cleavage, which prevents toxic A β peptide generation [110]. All of the enzymes involved in APP processing are transmembrane proteins, raising the hypothesis that the lipid composition and lipid organization in the membrane may affect A β production [111]. Numerous *in vitro* studies have focused on determining the role of specific lipid classes in APP processing. For example, it has been shown that reducing membrane cholesterol lowers the levels and activity of β -secretase and reduces γ -secretase activity, decreasing A β production [99, 112]. Altered cholesterol content in lipid rafts, regions in the cellular membrane enriched with cholesterol and sphingolipids, affects the localization of enzymes involved in A β production, which can lead to changes in amyloidogenic APP processing [99]. Moreover, sphingolipids have been reported to regulate γ -secretase activity [99, 113, 114]. Interestingly, expression of familial presenilin (PS) mutations, which are mutations in components of the γ -secretase complex, affects sphingolipid metabolism, suggesting an interplay of genetics and lipid metabolism in the context of APP processing. Furthermore, *in vitro* elevation of ceramide, which is composed of sphingosine and fatty acids, increases β -secretase stability and promotes A β biogenesis [115].

The production of A β peptides is not unique to AD pathology, but a constitutive process that is a product of normal cell metabolism throughout life, confirmed by its secretion from primary cells in culture and its presence in the plasma and CSF of healthy individuals [108, 116, 117]. Therefore, it is possible that disrupted A β homeostasis, either via increased production or impaired degradation and clearance, leads to its net accumulation in the brain, triggering subsequent neurotoxicity. A β production is clearly enhanced in cases of familial early onset AD (<60 years of age), which account for 2-3% of the AD population [118]. In contrast to familial early-onset AD cases, the vast majority of AD subjects who develop cognitive impairment in late life have no genetically-determined net increase in A β production. For these late-onset AD patients, who account for up to 99% of the AD population [119], aging, environmental factors, or other genetic-related impairments in A β degradation and clearance are thought to lead to the net accumulation of A β within the CNS [120-122].

3.2. Apolipoproteins and AD pathogenesis

Of the apolipoproteins present in the CNS, *APOE* has the most established genetic association with AD, influencing the risk, progression, and pathology of the disease (Table 1). The *APOE4* allele is a robust risk factor for late-onset AD and is found in 40-60% of AD subjects depending on ethnicity (the prevalence is lower in Asian compared to Northern European populations) even though its carrier frequency in the human population is approximately 15-20% [123-125]. *APOE4* increases AD risk by 3-fold when inherited in a single copy and greater than 9-fold in homozygous individuals. *APOE4* also accelerates the age of onset of AD [123, 126, 127]. A wealth of pre-clinical and clinical evidence has demonstrated that *APOE4* is associated with earlier and more extensive A β and amyloid deposition, which is currently believed to result from a net impairment of A β degradation and clearance from the CNS [120, 128]. ApoE affects A β metabolism through multiple mechanisms, including transport of A β across the BBB, modulation of interstitial fluid (ISF) and CSF clearance pathways, effects on BBB integrity, and modulating the growth of A β oligomers and fibrils [129, 130]. Some studies suggest that the risk and severity of CAA is also increased in *APOE4* carriers [131, 132]. Intriguingly, a patient with an ablative mutation in *APOE* was recently described to have no detectable impairment in cognitive, neurological and retinal function, with normal levels of CSF A β and tau despite very high plasma cholesterol levels [133], suggesting that apoE may have non-essential functions in the human brain and eye. This observation reflects the prediction made from *ApoE*-deficient mice, which also have greatly increased plasma cholesterol levels and exhibit greatly reduced A β retention in the CNS [134-137].

In addition to modulating A β , apoE may also be involved in tau phosphorylation. In neurons, hyperphosphorylation of the microtubule-associated protein tau by kinases, including GSK-3 β and CDK5, causes the dissociation and aggregation of tau to ultimately form neurofibrillary tangles [138]. Under conditions of stress or injury, neurons have been reported to synthesize and process apoE4 to produce neurotoxic C-terminal fragments. Release of these fragments into the neuronal cytosol has been reported to enhance tau phosphorylation and formation of NFT-like structures [139, 140].

ApoE4 has additional deleterious consequences. Compared to apoE3, apoE4 is less effective at mediating cholesterol transport in the brain; human knock-in *APOE4* homozygous mice show reduced total cholesterol and phospholipids compared to wild type mice [81, 141]. The *APOE4* allele has also been implicated in impaired synaptic integrity, as human *APOE4* transgenic mice show lower levels of excitatory synaptic activity that declines to levels comparable to *ApoE* knockout mice by 7 months of age [142]. ApoE4 has also been reported to reduce apoER2 expression at the neuronal surface, impairing the ability of Reelin to enhance synaptic glutamate receptor activity [143].

ApoE plays an integral role in inflammatory processes in the brain. Inflammation of the brain's glial supporting cells, known as neuroinflammation, is a prominent feature AD [144] and contributes to neuronal damage. In response to A β or lipopolysaccharide (LPS), LRP1-mediated glial cell activation increases apoE, which can limit the inflammatory response by signaling through LDL receptors to suppress c-Jun N-terminal kinase signaling [145, 146]. There is also evidence that isoform-specific apoE modulation of the innate immune response can

modulate A β deposition [147]. Consistent with apoE having an anti-inflammatory role, *ApoE*-deficient mice have elevated proinflammatory cytokines in the liver [148]. Importantly, isoform specific effects appear to determine the extent of cytokine induction and may also modulate progression and resolution of CNS inflammation. In mice, apoE4 has reduced ability to suppress the inflammatory response induced by LPS treatment [149] and in the EFAD model (5 familial AD mutations in the presence of human *APOE*), microglial activation in response to A β is augmented by the *APOE4* genotype [150]. Indeed, *ApoE*-deficient mice show a similar activation of the inflammatory response to human *APOE4* knock-in mice following LPS injection, implying that apoE4 may lack the anti-inflammatory functions of the other apoE isoforms [151]. Consistent with these findings, non-steroidal anti-inflammatory drugs are associated with a reduced risk of AD only in participants with an *APOE4* allele [152].

According to the AlzGene database, *CLU* is the third most highly associated susceptibility locus for AD following *APOE* and bridging integrator 1 (*BINI*) (www.alzgene.org). In 2009, two independent GWAS studies identified the C allele of the rs11136000 SNP in the *CLU* gene, which occurs in 88% of Caucasians, to confer a modest risk of AD development (odds ratio (OR) 1.16), whereas inheritance of the T allele is protective (OR 0.86) in Caucasians [153, 154]. Although these findings have been replicated in, and confirmed for, Caucasians of European ancestry, the association of *CLU* polymorphisms and AD risk has not been replicated in African-American, Hispanic, or Arab populations [27, 155]. Since this discovery, extensive work has been conducted in an attempt to delineate the mechanism(s) by which the rs11136000 SNP confers AD risk. Inheritance of the TT versus TC versus CC allele appears to result in either no change [156, 157] or a very subtle 8% decrease [158] of plasma clusterin levels in AD and mild cognitive impairment (MCI) patients, with small 10-17% decreases of plasma clusterin observed in cognitively normal aged-matched controls with the TT allele [156, 158]. Despite minimal effects on circulating clusterin levels with the T allele, inheritance of the C allele of the rs11136000 SNP is associated with both structural and functional changes in the CNS. In young (aged 20-30 years) cognitively normal adults, each copy of the C allele of the rs11136000 SNP is associated with lower white matter integrity [159], decreased coupling and connectivity between the hippocampus and prefrontal cortex during memory processing tasks [160], and neural hyperactivity under emotional working paradigms [161], indicative of early structural and functional abnormalities that may leave the brain more vulnerable to disease during aging. In the elderly, independent of dementia status, the CC allele is significantly associated with longitudinal increases in ventricular volume over a 2 year period [162], and increased resting regional cerebral blood flow in the hippocampus and right anterior cingulate cortex, regions which are important for memory function and default mode network activity, over an 8-year period [163]. Further, the protective T allele is associated with a reduced rate of conversion from MCI to AD (OR 0.25) [164], while the detrimental C allele is correlated with a significantly faster rate of decline in verbal but not visual memory performance in MCI and AD patients [163]. Lastly, with respect to CSF biomarkers, the *CLU* C allele is associated with significantly lower CSF A β 42 in a Finnish [165] but not American cohort [166], with no association found for either total or phosphorylated tau.

Although the specific mechanisms by which an individual SNP in *CLU* may confer disease risk are not well understood, there are well recognized global changes to clusterin mRNA and protein expression both in the plasma and CNS that are associated with AD pathology and clinical presentation [27]. In non-demented elderly controls and patients with subjective memory complaints, CSF clusterin is positively associated with CSF total and phosphorylated tau [167] and an elevated atrophy rate in the entorhinal cortex of older non-demented adults with low CSF A β 42 [168]. Whereas older studies did not detect significant differences in CSF clusterin between cognitively normal aged matched controls and AD subjects [25, 169], newer studies that utilize higher sensitivity methods have reported up to a 25% increase of CSF clusterin in AD subjects [170, 171], suggesting that increased CNS clusterin may be detrimental. Within brain tissue, clusterin mRNA is increased after correcting for neuronal loss [172, 173], whereas protein levels are reportedly increased by 40-180% depending on the brain region [172, 174-177]. Within the AD brain, clusterin strongly co-stains with dystrophic neurites, neuropil threads, and intracellular NFT [176, 178, 179], with minimal to moderate co-localization observed with mature amyloid plaques [176, 178, 180, 181] and cerebrovascular amyloid [180]. Unlike the CNS, multiple studies have detected no difference between plasma clusterin levels in non-demented controls, MCI, and AD subjects [157, 182-185]. However, increased baseline plasma clusterin levels are suggestive of increased prevalence and severity of AD pathology and presentation, including brain atrophy, amyloid deposition and worsened cognitive function, with a more rapid clinical progression [186-188].

A mechanistic involvement of clusterin in AD pathology is also supported by *in vivo* preclinical studies (Table 1) [27]. Clusterin appears to be directly involved in neuronal health and A β metabolism via a variety of mechanisms. In transgenic AD mice, genetic ablation of clusterin results in a reduction of mature fibrillar amyloid deposits and the dystrophic neurites that are associated with them [189]. Supporting this, a recent study found that co-incubation of A β with clusterin leads to a 60% decrease in oligomeric and 42% decrease in fibrillar A β binding and uptake by primary microglia, and a 72% reduction in binding and uptake of oligomeric A β by primary astrocytes, suggesting that clusterin can impede A β degradation by local glia [190]. *In vitro* and *in vivo*, clusterin may also mediate A β toxicity and tau phosphorylation via dickkopf-1-driven induction of the Wnt-PCP-JNK pathway [191]. In contrast, other studies have found a beneficial role of clusterin in facilitating A β clearance across the BBB via LRP-2 [192] and binding to and sequestering A β oligomers, thereby reducing their potential toxicity [193]. Clusterin also participates in various aspects of cell signaling. *In vitro*, clusterin signals via Reelin by binding to apoER2 and VLDLR thereby increasing cell proliferation and neuroblast chain formation in the subventricular zone [77]. Clearly, more research is necessary to fully understand the pathways by which clusterin is involved in brain function and the pathogenesis of AD.

Although apoA-I is relatively abundant in CSF and brain tissue, the physiological roles of apoA-I containing lipoprotein particles in the CNS, their potential influence on AD risk and pathology, and whether they affect AD pathogenesis through actions from one or both sides of the BBB remains unknown [14]. The most established data regarding apoA-I and AD are human epidemiological studies examining the interaction between serum apoA-I and HDL-

cholesterol levels with AD risk (Table 1). At mid-life, high serum apoA-I levels resulted in a significantly lower risk (hazard ratio (HR) 0.25) of dementia later in life, [194] while high levels of serum HDL cholesterol (> 55 mg/dL) in cognitively normal elderly was associated with a significantly reduced risk (HR 0.4) of AD even after adjusting for *APOE* genotype and vascular risk factors such as heart disease, diabetes, obesity, hypertension, and lipid lowering treatment [195]. Recently, Reed et al. demonstrated that low plasma HDL cholesterol and apoA-I were associated with and predicted higher amyloid Pittsburgh compound B binding independent of *APOE4* in cognitively normal and MCI elderly subjects [196]. There also appears to be a consistent 20-30% reduction in serum apoA-I in late-onset AD subjects compared to age-matched controls [197-199], with levels of serum apoA-I positively correlating to cognitive function [199, 200]. Further, in symptomatic AD patients, plasma apoA-I levels are negatively correlated with measures of brain atrophy, including hippocampal and whole brain volume and mean entorhinal thickness [186]. Alterations to CSF apoA-I are less clear, potentially due to the small number of studies or sample size, whereas two studies reported a decrease of CSF apoA-I in AD subjects [15, 201], two other studies reported no change [13, 202]. Prospective studies designed and powered to assess the levels, and perhaps more importantly, the function of both plasma and CSF apoA-I-HDL with respect to AD onset and progression are needed to determine if apoA-I-HDL potentially contributes to AD pathology.

Although questions remain about the importance of apoA-I to AD in humans, studies in preclinical AD mouse models support a role for apoA-I in removing amyloid selectively from the cerebral vasculature, leading to reduced neuroinflammation and maintenance of cognitive function (Table 1). Specifically, genetic loss of *Apoa1* is associated with increased CAA, greater inflammation, and exacerbated cognitive impairment, whereas transgenic overexpression of human *APOA1* from its endogenous promoter (driving expression from only hepatocytes and enterocytes) prevented AD-related cognitive decline and reduced both CAA and glial activation in symptomatic APP/PS1 mice [203, 204]. Given the known roles of apoA-I-containing HDL in regulating vascular endothelial health, reducing inflammation and oxidative stress, coupled with the relative contributions of these pathologies to AD, it will be paramount to fully elucidate the function of apoA-I in the CNS and evaluate its therapeutic potential [14].

Although the roles of other CNS apolipoproteins in AD pathogenesis are not as extensively studied, apoD, apoC-I, apoA-IV, and apoC-III may play a role. The most significant change due to aging is observed in gene expression levels of *APOD* [205]; CSF and hippocampal apoD are elevated in AD [206] and correlated with disease severity [207]. ApoC-I colocalizes with A β plaques in human AD brain [208] and apoC-I has been suggested to influence neuroinflammation in AD [209]. The *APOC1* gene is also considered as an AD susceptibility locus, as the H2 polymorphism of *APOC1* is in linkage disequilibrium with *APOE4* [209-211]. Furthermore, heterozygosity of the *APOA4* (360:His) allele is more common in AD patients [212]. In APP transgenic mice, *Apoa4* deficiency increases A β load, enhances neuronal loss, accelerates cognitive dysfunction and increases mortality [213]. Lastly, apoC-III has recently been reported to be associated with A β levels in the periphery and is of possible interest for use as an early biomarker for AD [214].

3.3. Cholesterol and phospholipid transporters in AD

There is a growing body of pre-clinical and clinical evidence that supports the involvement of ABCA1, and recently ABCA7, in the pathogenesis of AD [215]. In mice, ABCA1-mediated lipidation of apoE correlates with a net increase in A β clearance [216]. For example, total body deficiency of *Abca1* markedly decreases soluble apoE and increases amyloid plaque-associated insoluble apoE, decreases plasma and CSF apoA-I, and increases A β deposits in both parenchymal and vascular compartments, with no net change in APP production or processing [217-220]. Recently, Fitz et al. demonstrated that haploinsufficiency of *Abca1* significantly exacerbated cognitive deficits, increased A β and amyloid deposits, and reduced A β clearance in ISF of *APOE4* but not *APOE3* APP/PS1 *Abca1*^{-/+} mice, suggesting a particularly deleterious state of poorly-lipidated apoE4 compared to apoE3 [221]. Of interest, the presence of apoE4 with *Abca1* hemizyosity leads to a modest but statistically significant decrease in CNS apoE (~10%), decreased CNS and plasma apoA-I by approximately 50 and 20%, respectively, and decreased plasma A β 42 and HDL cholesterol, with a strong inverse correlation between plasma HDL cholesterol levels and amyloid burden [221]. Both genetic and pharmacological approaches that increase brain ABCA1 activity also increase functional CNS apoE [40, 222] and improve learning and memory with [222-227] or without [228-232] changes in A β and/or amyloid burden. Importantly, ABCA1 was required to observe an improvement in cognitive function in APP/PS1 mice treated with the LXR agonist GW3965, suggesting that ABCA1 lipidation of lipid-poor apolipoproteins is essential for cognitive function [229]. It is important to note, however, that these manipulations will affect ABCA1-mediated lipidation of apoE in the brain as well as ABCA1-mediated lipidation of apoA-I in the periphery and potentially the CNS, of which the relative contributions are unknown.

The association of *ABCA1* genetic variants and AD risk in human subjects is not as clear despite more than a dozen studies [216]. In 2013, a meta-analysis was conducted on 13 independent studies totaling 6034 controls and 6214 AD patients that examined whether the *ABCA1* variants R219K rs2230806, I883M rs4149313 and R1587K rs2230808 were associated with AD risk. No significant association was found even after adjusting by ethnicity and sample size [233]. This is consistent with *ABCA1* failing to appear in GWAS [216]. It is important to note, however, that most of the *ABCA1* gene variants in heterozygous patients translate to a relatively small reduction in plasma HDL cholesterol that may or may not increase the relative risk of ischemic heart disease [234, 235], raising the caveat that these variants may not be severe enough to impact brain physiology. As Tangier Disease, in which patients completely lack functional ABCA1, is extremely rare and most patients die before 70 years of age, it is not known whether human ABCA1 deficiency is associated with neuropathological changes relevant to AD [236].

In contrast to ABCA1, numerous independent GWAS have identified associations between multiple *ABCA7* SNPs and AD risk [237-244]. *ABCA7* expression has been reported to be increased in the brains of AD subjects, with the magnitude of the increase correlating with greater cognitive decline [239, 241]. In 2011, the first two major SNPs of *ABCA7*, rs2764650 [244] and rs3752246 [237], were associated with increased risk of late-onset AD. Two subsequent GWAS found that the rs2764650 SNP was significantly associated with increased neuritic plaque burden [242, 243]. However, both Larch et al. and Vas-

quez et al. found that the minor allele of the rs2764650 SNP conferred protection from AD by delaying onset and decreasing disease duration, despite increased ABCA7 expression, whereas another study found that rs2764650 neither altered ABCA7 expression or AD risk [238]. In African Americans, the ABCA7 rs115550680 SNP was shown to increase AD risk by 1.79 even after adjusting for APOE genotype, which itself conferred a relative risk of 2.31 [240]. With more ABCA7 SNPs identified by GWAS to confer AD risk [238], it will be increasingly important to identify the functional consequences of ABCA7 polymorphisms. In transgenic APP mice, total body loss of *Abca7* increases hippocampal A β and amyloid burden with no changes in APP processing or brain levels of ABCA1, apoE, LDLR, or markers of neurodegeneration or synaptic loss [245]. However, increased A β and amyloid did not significantly impair any measure of cognitive function, including spatial memory, object recognition, short-term recognition, or fear conditioning [245]. Intriguingly, bone marrow derived macrophages obtained from *Abca7*^{-/-} mice displayed a 50% reduction in A β uptake compared to wild type controls, suggesting that phagocytosis may be compromised; however, there were no change to either the number or distribution of microglia or macrophages within the brain parenchyma in AD *Abca7*^{-/-} mice [245].

Despite high expression in the brain, ABCG1 does not appear to have a marked role in AD pathogenesis, as ABCG1 overexpression in AD mice does not significantly change A β or amyloid burden [246]. Although a recent GWAS study reported that ABCG1 SNPs were correlated with neuritic plaque burden in AD subjects [243], the relative risk of ABCG1 variants has yet to be confirmed.

3.4. LCAT, PLTP and CETP in AD

Although better characterized with respect to their involvement in atherosclerosis, research is emerging regarding the potential role of the lipoprotein modifying enzymes LCAT, PLTP and CETP in AD [53, 65, 247]. One early study in a small group of symptomatic AD patients suggested that CSF LCAT activity was reduced by 50% compared to cognitively normal age-matched controls [13], raising the possibility that aging may influence LCAT activity or LCAT activity may influence AD pathogenesis. Stukas et al. recently tested this hypothesis in mice and found that the abundance and activity of LCAT in liver, cortex and plasma is unaltered by aging or the presence of amyloid deposits [14]. Furthermore, total loss of *Lcat* does not impact apoE levels or lipidation, or A β or amyloid metabolism in symptomatic APP/PS1 mice, despite a 70-90% decrease in circulating and CNS levels of apoA-I [14]. These results suggest that CNS lipoproteins need not be in a mature spherical form containing cholesterol esters to participate normally in A β metabolism.

PLTP may also be involved in the pathogenesis of AD. Intriguingly, whereas PLTP synthesis by neurons and glia is increased in the early stages of AD [62], its levels, and more importantly, its activity are reduced in brain tissue and CSF of AD patients in later stages [57, 63]. In mice, deletion of *Pltp* increases cerebral oxidative stress, elevates A β ₄₂, reduces synaptophysin expression, increases BBB permeability and decreases expression of tight junction proteins under basal conditions [61, 248]. Further, intracerebroventricular injection of an oligomeric A β peptide leads to exacerbated cognitive impairment in *Pltp*^{-/-} mice compared to wild-type

controls [248]. In aged *Pltp*^{-/-} mice, enhanced cognitive impairment is accompanied by increased cortical A β 42, APP expression, and both β - and γ -secretase activity with decreases in cortical A β 40 and apoE [249]. These preclinical studies suggest a role for PLTP not only in phospholipid transport, but A β homeostasis, neuronal function, barrier integrity, and oxidative stress.

Another enzyme that plays a central role in lipid homeostasis that can potentially affect dementia outcome is CETP. As reduced CETP activity in humans is associated with reduced cardiovascular disease risk, the functions of CETP in atherosclerosis and the potential of CETP inhibitors for cardiovascular disease have been of intense interest [65]. The *CETP* 405V allele, which results in low plasma CETP levels in *CETP* 405V homozygotes [250], is associated with longevity. However, the direction and the magnitude of this effect is not clear as some studies have found a positive association, some a negative association, and some no association with longevity [251-256]. It has also been shown that in young adults, this allele is associated with higher fractional anisotropy, a measure of myelination in brain's white matter [257]. In older subjects, however, this effect is reversed [257]. Furthermore, genetic studies have proposed a relationship between C629A, I405V, and D442G *CETP* polymorphisms and AD risk. Intriguingly, the effects that are exerted by these polymorphisms may be dependent on the presence of the *APOE4* allele. Rodriguez et al. reported that in *APOE4* carriers, the AA genotype of the C629A *CETP* polymorphism is associated with lower AD risk [258]. It has also been shown that in the Northern Han Chinese population, there is an association between the G allele of the D442G *CETP* polymorphism and lower AD risk, an effect that was abolished in the absence of *APOE4* [259]. Additionally, Murphy et al. reported that in *APOE4* non-carriers, the I allele of the I405V polymorphism is protective, whereas the V allele is associated with higher AD risk [260]. Interestingly, these associations are reversed in *APOE4* carriers [260]. These results are replicated by the Rotterdam study [250]. However, the Einstein Aging Study reported an association between the VV genotype and slower memory decline and AD risk, and a recent meta-analysis by Li et al. reported no association between AD and the I405V *CETP* polymorphism [253, 261]. Clearly, more research is required to elucidate the specific role of CETP in the brain and its contribution to AD.

3.5. ApoE receptors

APP endocytosis is regulated by several members of the lipoprotein receptor family leading to increased or reduced A β generation [74]. These receptors are also critical for A β clearance. LRP1 can bind A β directly or bind apoE-associated A β to internalize and transport soluble A β across the BBB to plasma for eventual degradation, or mediate degradation within cell lysosomes [262-266]. *APOE* genotype impacts clearance of A β -apoE complexes with A β -apoE4 having the slowest net clearance rate [267]. Findings in knockout mice imply LDLR may also enhance A β clearance [268, 269]. Other apolipoproteins such as clusterin may play a role in mediating A β degradation and clearance through the LDLR family of receptors [83]. In addition to A β removal, apoE receptors also regulate tau phosphorylation. Reelin signaling through apoER2 and VLDLR inhibits the activity of GSK-3 β and blockade of this pathway increases hyperphosphorylated tau in the brain [270, 271]. Although apoE receptors are clearly impli-

cated in AD pathogenesis by a number of mechanisms, genetic evidence for their role is not robust, despite mutations in *LDLR* being highly associated with hypercholesterolemia in humans [272]. For example, a polymorphism in exon 3 of the *LRP1* gene (rs1799986) has been weakly correlated with increased risk of AD, although subjects with both this *LRP1* allele and a tau polymorphism (*MAPT*, intron 9, rs2471738) have 6.2-fold higher risk of developing AD than those without this genotype [273-275]. A polymorphism in *LRP2* (rs3755166) has also been reported to be associated with AD [276, 277]. By contrast, the neuronal sortilin-related receptor (*SORL1*, also known as *LR11*) is an apoE receptor that has been shown to be significantly associated with AD risk by multiple groups and in a GWAS [278, 279]. *SORL1* levels are reduced in AD brains [280] and risk variants that decrease *SORL1* expression, particularly in childhood and adolescence, predict increases in amyloid pathology [281].

4. Conclusions and future directions

ApoE is the major apolipoprotein produced within the CNS and is intimately involved in the risk, progression, and pathogenesis of AD. Allelic differences in *APOE* appear to confer isoform specific effects with respect to A β deposition, degradation and clearance, tau phosphorylation, neuronal injury and inflammation. Given its gain of toxic or loss of beneficial function, strategies aimed at increasing functional apoE may be of therapeutic interest, although it is possible that elevated levels of dysfunctional apoE4 may actually be detrimental for *APOE4* carriers. However, as over 50% of AD patients carry at least one *APOE4* allele, development of future therapies must take into account the structural and functional differences of this lipoprotein isoform, and seek to develop ways to either correct or bypass the “dysfunction” of apoE4. Long ignored, the importance of clusterin in CNS health and disease is now rapidly expanding. While clinical evidence is mounting that clusterin may be involved in AD disease risk, severity, and rate of decline both with respect to cognitive function and A β metabolism, the mechanism(s) by which clusterin confers these roles is poorly understood. ApoA-I may also influence AD pathology, potentially by modulating cerebrovascular integrity and function by assisting in the removal of A β peptides from cerebrovascular smooth muscle cells and decreasing inflammation. Indeed, the known effects of common AD comorbidities such as type II diabetes and hypercholesterolemia, on apoA-I function, should be taken into account in clinical studies on dementia risk and potential therapeutic approaches.

In the cardiovascular field, many preclinical and clinical studies have endeavored to increase the net concentration of circulating HDL to protect against cardiovascular disease. Many of these studies may also have implications for CNS function. However, as some of these approaches, such as the inhibition of CETP, have failed to meet their primary endpoints for cardiovascular disease despite significantly increasing HDL cholesterol levels, the lipoprotein field is now deeply invested in understanding the functional complexities of HDL. Therapeutic interventions aimed at increasing the function of HDL particles and their cargo may be of much greater importance than increasing its net levels, in both the peripheral and CNS compartments. Given the complexity of the HDL proteome and lipidome, it will be critical to divest the same details in the CNS to allow for therapeutic development targeting lipoprotein species.

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References

- [1] Dietschy JM. Central nervous system: cholesterol turnover, brain development and neurodegeneration. *Biological chemistry*. 2009 Apr;390(4):287-93.
- [2] Lim L, Wenk MR. Neuronal Membrane Lipids – Their Role in the Synaptic Vesicle Cycle. In: Tettamanti GG, G., editor. *Handbook of Neurochemistry and Molecular Neurobiology*. New York: Springer Science+Business Media; 2009. p. 223 - 38.
- [3] Vance JE, Hayashi H. Formation and function of apolipoprotein E-containing lipoproteins in the nervous system. *Biochimica et biophysica acta*. 2010 Aug;1801(8):806-18.
- [4] Beffert U, Danik M, Krzywkowski P, Ramassamy C, Berrada F, Poirier J. The neurobiology of apolipoproteins and their receptors in the CNS and Alzheimer's disease. *Brain research Brain research reviews*. 1998 Jul;27(2):119-42.
- [5] Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH. 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. *The Journal of biological chemistry*. 1987 Oct 15;262(29):14352-60.
- [6] Ladu MJ, Reardon C, Van Eldik L, Fagan AM, Bu G, Holtzman D, et al. Lipoproteins in the central nervous system. *Annals of the New York Academy of Sciences*. 2000 Apr;903:167-75.
- [7] LaDu MJ, Gilligan SM, Lukens JR, Cabana VG, Reardon CA, Van Eldik LJ, et al. Nascent astrocyte particles differ from lipoproteins in CSF. *Journal of neurochemistry*. 1998 May;70(5):2070-81.
- [8] Koch S, Donarski N, Goetze K, Kreckel M, Stuerenburg HJ, Buhmann C, et al. Characterization of four lipoprotein classes in human cerebrospinal fluid. *Journal of lipid research*. 2001 Jul;42(7):1143-51.
- [9] Borghini I, Barja F, Pometta D, James RW. Characterization of subpopulations of lipoprotein particles isolated from human cerebrospinal fluid. *Biochimica et biophysica acta*. 1995 Mar 16;1255(2):192-200.

- [10] DeMattos RB, Brendza RP, Heuser JE, Kierson M, Cirrito JR, Fryer J, et al. Purification and characterization of astrocyte-secreted apolipoprotein E and J-containing lipoproteins from wild-type and human apoE transgenic mice. *Neurochemistry international*. 2001 Nov- Dec;39(5-6):415-25.
- [11] Roheim PS, Carey M, Forte T, Vega GL. Apolipoproteins in human cerebrospinal fluid. *Proceedings of the National Academy of Sciences of the United States of America*. 1979 Sep;76(9):4646-9.
- [12] Fan J, Shimizu Y, Chan J, Wilkinson A, Ito A, Tontonoz P, et al. Hormonal modulators of glial ABCA1 and apoE levels. *Journal of lipid research*. 2013 Nov;54(11):3139-50.
- [13] Demeester N, Castro G, Desrumaux C, De Geitere C, Fruchart JC, Santens P, et al. Characterization and functional studies of lipoproteins, lipid transfer proteins, and lecithin:cholesterol acyltransferase in CSF of normal individuals and patients with Alzheimer's disease. *Journal of lipid research*. 2000 Jun;41(6):963-74.
- [14] Stukas S, Robert J, Wellington CL. High Density Lipoproteins and Cerebrovascular Integrity in Alzheimer's Disease. *Cell metabolism*. 2014.
- [15] Roher AE, Maarouf CL, Sue LI, Hu Y, Wilson J, Beach TG. Proteomics-derived cerebrospinal fluid markers of autopsy-confirmed Alzheimer's disease. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals*. 2009 Nov;14(7):493-501.
- [16] Wahrle SE, Shah AR, Fagan AM, Smemo S, Kauwe JS, Grupe A, et al. Apolipoprotein E levels in cerebrospinal fluid and the effects of ABCA1 polymorphisms. *Molecular neurodegeneration*. 2007;2:7.
- [17] Ulrich JD, Burchett JM, Restivo JL, Schuler DR, Verghese PB, Mahan TE, et al. In vivo measurement of apolipoprotein E from the brain interstitial fluid using microdialysis. *Molecular neurodegeneration*. 2013;8:13.
- [18] Fagan AM, Holtzman DM, Munson G, Mathur T, Schneider D, Chang LK, et al. Unique lipoproteins secreted by primary astrocytes from wild type, apoE (-/-), and human apoE transgenic mice. *The Journal of biological chemistry*. 1999 Oct 15;274(42):30001-7.
- [19] Dorey E, Chang N, Liu QY, Yang Z, Zhang W. Apolipoprotein E, amyloid-beta, and neuroinflammation in Alzheimer's disease. *Neuroscience bulletin*. 2014 Apr;30(2):317-30.
- [20] Hirsch-Reinshagen V, Zhou S, Burgess BL, Bernier L, McIsaac SA, Chan JY, et al. Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain. *The Journal of biological chemistry*. 2004 Sep 24;279(39):41197-207.

- [21] Wahrle SE, Jiang H, Parsadanian M, Legleiter J, Han X, Fryer JD, et al. ABCA1 is required for normal central nervous system ApoE levels and for lipidation of astrocyte-secreted apoE. *The Journal of biological chemistry*. 2004 Sep 24;279(39):40987-93.
- [22] Hatters DM, Peters-Libeu CA, Weisgraber KH. Apolipoprotein E structure: insights into function. *Trends in biochemical sciences*. 2006 Aug;31(8):445-54.
- [23] Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature reviews Neurology*. 2013 Feb;9(2):106-18.
- [24] de Silva HV, Harmony JA, Stuart WD, Gil CM, Robbins J. Apolipoprotein J: structure and tissue distribution. *Biochemistry*. 1990 Jun 5;29(22):5380-9.
- [25] Lidstrom AM, Hesse C, Rosengren L, Fredman P, Davidsson P, Blennow K. Normal levels of clusterin in cerebrospinal fluid in Alzheimer's disease, and no change after acute ischemic stroke. *Journal of Alzheimer's disease : JAD*. 2001 Oct;3(5):435-42.
- [26] Rizzi F, Coletta M, Bettuzzi S. Chapter 2: Clusterin (CLU): From one gene and two transcripts to many proteins. *Advances in cancer research*. 2009;104:9-23.
- [27] Yu JT, Tan L. The role of clusterin in Alzheimer's disease: pathways, pathogenesis, and therapy. *Molecular neurobiology*. 2012 Apr;45(2):314-26.
- [28] Elshourbagy NA, Boguski MS, Liao WS, Jefferson LS, Gordon JI, Taylor JM. Expression of rat apolipoprotein A-IV and A-I genes: mRNA induction during development and in response to glucocorticoids and insulin. *Proceedings of the National Academy of Sciences of the United States of America*. 1985 Dec;82(23):8242-6.
- [29] Zannis VI, Cole FS, Jackson CL, Kurnit DM, Karathanasis SK. Distribution of apolipoprotein A-I, C-II, C-III, and E mRNA in fetal human tissues. Time-dependent induction of apolipoprotein E mRNA by cultures of human monocyte-macrophages. *Biochemistry*. 1985 Jul 30;24(16):4450-5.
- [30] Karasinska JM, Rinninger F, Lutjohann D, Ruddle P, Franciosi S, Kruit JK, et al. Specific loss of brain ABCA1 increases brain cholesterol uptake and influences neuronal structure and function. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009 Mar 18;29(11):3579-89.
- [31] Stukas S, Robert J, Lee M, Kulic I, Carr M, Tourigny K, et al. Intravenously injected human apolipoprotein A-I rapidly enters the central nervous system via the choroid plexus. *Journal of the American Heart Association*. Forthcoming 2014.
- [32] Kratzer I, Wernig K, Panzenboeck U, Bernhart E, Reicher H, Wronski R, et al. Apolipoprotein A-I coating of protamine-oligonucleotide nanoparticles increases particle uptake and transcytosis in an in vitro model of the blood-brain barrier. *Journal of controlled release : official journal of the Controlled Release Society*. 2007 Feb 26;117(3):301-11.

- [33] Song H, Seishima M, Saito K, Maeda S, Takemura M, Noma A, et al. Apo A-I and apo E concentrations in cerebrospinal fluids of patients with acute meningitis. *Annals of clinical biochemistry*. 1998 May;35 (Pt 3):408-14.
- [34] Navarro A, Tolivia J, Astudillo A, del Valle E. Pattern of apolipoprotein D immunoreactivity in human brain. *Neuroscience letters*. 1998 Sep 18;254(1):17-20.
- [35] Dassati S, Waldner A, Schweigreiter R. Apolipoprotein D takes center stage in the stress response of the aging and degenerative brain. *Neurobiology of aging*. 2014 Jul; 35(7):1632-42.
- [36] Koldamova RP, Lefterov IM, Ikonomovic MD, Skoko J, Lefterov PI, Isanski BA, et al. 22R-hydroxycholesterol and 9-cis-retinoic acid induce ATP-binding cassette transporter A1 expression and cholesterol efflux in brain cells and decrease amyloid beta secretion. *The Journal of biological chemistry*. 2003 Apr 11;278(15):13244-56.
- [37] Kim WS, Rahmanto AS, Kamili A, Rye KA, Guillemin GJ, Gelissen IC, et al. Role of ABCG1 and ABCA1 in regulation of neuronal cholesterol efflux to apolipoprotein E discs and suppression of amyloid-beta peptide generation. *The Journal of biological chemistry*. 2007 Feb 2;282(5):2851-61.
- [38] Panzenboeck U, Balazs Z, Sovic A, Hrzenjak A, Levak-Frank S, Wintersperger A, et al. ABCA1 and scavenger receptor class B, type I, are modulators of reverse sterol transport at an in vitro blood-brain barrier constituted of porcine brain capillary endothelial cells. *The Journal of biological chemistry*. 2002 Nov 8;277(45):42781-9.
- [39] Saint-Pol J, Vandenhoute E, Boucau MC, Candela P, Dehouck L, Cecchelli R, et al. Brain pericytes ABCA1 expression mediates cholesterol efflux but not cellular amyloid-beta peptide accumulation. *Journal of Alzheimer's disease : JAD*. 2012;30(3): 489-503.
- [40] Stukas S, May S, Wilkinson A, Chan J, Donkin J, Wellington CL. The LXR agonist GW3965 increases apoA-I protein levels in the central nervous system independent of ABCA1. *Biochimica et biophysica acta*. 2012 Mar;1821(3):536-46.
- [41] Kim WS, Guillemin GJ, Glaros EN, Lim CK, Garner B. Quantitation of ATP-binding cassette subfamily-A transporter gene expression in primary human brain cells. *Neuroreport*. 2006 Jun 26;17(9):891-6.
- [42] Wang N, Lan D, Gerbod-Giannone M, Linsel-Nitschke P, Jehle AW, Chen W, et al. ATP-binding cassette transporter A7 (ABCA7) binds apolipoprotein A-I and mediates cellular phospholipid but not cholesterol efflux. *The Journal of biological chemistry*. 2003 Oct 31;278(44):42906-12.
- [43] Kim WS, Fitzgerald ML, Kang K, Okuhira K, Bell SA, Manning JJ, et al. Abca7 null mice retain normal macrophage phosphatidylcholine and cholesterol efflux activity despite alterations in adipose mass and serum cholesterol levels. *The Journal of biological chemistry*. 2005 Feb 4;280(5):3989-95.

- [44] Iwamoto N, Abe-Dohmae S, Sato R, Yokoyama S. ABCA7 expression is regulated by cellular cholesterol through the SREBP2 pathway and associated with phagocytosis. *Journal of lipid research*. 2006 Sep;47(9):1915-27.
- [45] Tanaka N, Abe-Dohmae S, Iwamoto N, Fitzgerald ML, Yokoyama S. Helical apolipoproteins of high-density lipoprotein enhance phagocytosis by stabilizing ATP-binding cassette transporter A7. *Journal of lipid research*. 2010 Sep;51(9):2591-9.
- [46] Wang N, Lan D, Chen W, Matsuura F, Tall AR. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. *Proceedings of the National Academy of Sciences of the United States of America*. 2004 Jun 29;101(26):9774-9.
- [47] Tarr PT, Edwards PA. ABCG1 and ABCG4 are coexpressed in neurons and astrocytes of the CNS and regulate cholesterol homeostasis through SREBP-2. *Journal of lipid research*. 2008 Jan;49(1):169-82.
- [48] Wang N, Yvan-Charvet L, Lutjohann D, Mulder M, Vanmierlo T, Kim TW, et al. ATP-binding cassette transporters G1 and G4 mediate cholesterol and desmosterol efflux to HDL and regulate sterol accumulation in the brain. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2008 Apr;22(4):1073-82.
- [49] Albers JJ, Marcovina SM, Christenson RH. Lecithin cholesterol acyltransferase in human cerebrospinal fluid: reduced level in patients with multiple sclerosis and evidence of direct synthesis in the brain. *International journal of clinical & laboratory research*. 1992;22(3):169-72.
- [50] Warden CH, Langner CA, Gordon JI, Taylor BA, McLean JW, Lusis AJ. Tissue-specific expression, developmental regulation, and chromosomal mapping of the lecithin:cholesterol acyltransferase gene. Evidence for expression in brain and testes as well as liver. *The Journal of biological chemistry*. 1989 Dec 25;264(36):21573-81.
- [51] Yamada T, Kawata M, Arai H, Fukasawa M, Inoue K, Sato T. Astroglial localization of cholesteryl ester transfer protein in normal and Alzheimer's disease brain tissues. *Acta neuropathologica*. 1995;90(6):633-6.
- [52] Lagrost L, Athias A, Gamber P, Lallemand C. Comparative study of phospholipid transfer activities mediated by cholesteryl ester transfer protein and phospholipid transfer protein. *Journal of lipid research*. 1994 May;35(5):825-35.
- [53] Albers JJ, Vuletich S, Cheung MC. Role of plasma phospholipid transfer protein in lipid and lipoprotein metabolism. *Biochimica et biophysica acta*. 2012 Mar;1821(3):345-57.
- [54] Calabresi L, Simonelli S, Gomaschi M, Franceschini G. Genetic lecithin:cholesterol acyltransferase deficiency and cardiovascular disease. *Atherosclerosis*. 2012 Jun;222(2):299-306.

- [55] Hirsch-Reinshagen V, Donkin J, Stukas S, Chan J, Wilkinson A, Fan J, et al. LCAT synthesized by primary astrocytes esterifies cholesterol on glia-derived lipoproteins. *Journal of lipid research*. 2009 May;50(5):885-93.
- [56] Guyton JR, Miller SE, Martin ME, Khan WA, Roses AD, Strittmatter WJ. Novel large apolipoprotein E-containing lipoproteins of density 1.006-1.060 g/ml in human cerebrospinal fluid. *Journal of neurochemistry*. 1998 Mar;70(3):1235-40.
- [57] Albers JJ, Wolfbauer G, Cheung MC, Day JR, Ching AF, Lok S, et al. Functional expression of human and mouse plasma phospholipid transfer protein: effect of recombinant and plasma PLTP on HDL subspecies. *Biochimica et biophysica acta*. 1995 Aug 24;1258(1):27-34.
- [58] Chirackal Manavalan AP, Kober A, Metso J, Lang I, Becker T, Hasslitz K, et al. Phospholipid transfer protein is expressed in cerebrovascular endothelial cells and involved in high density lipoprotein biogenesis and remodeling at the blood-brain barrier. *The Journal of biological chemistry*. 2014 Feb 21;289(8):4683-98.
- [59] Gander R, Eller P, Kaser S, Theurl I, Walter D, Sauper T, et al. Molecular characterization of rabbit phospholipid transfer protein: choroid plexus and ependyma synthesize high levels of phospholipid transfer protein. *Journal of lipid research*. 2002 Apr;43(4):636-45.
- [60] Oslakovic C, Krisinger MJ, Andersson A, Jauhiainen M, Ehnholm C, Dahlback B. Anionic phospholipids lose their procoagulant properties when incorporated into high density lipoproteins. *The Journal of biological chemistry*. 2009 Feb 27;284(9):5896-904.
- [61] Zhou T, He Q, Tong Y, Zhan R, Xu F, Fan D, et al. Phospholipid transfer protein (PLTP) deficiency impaired blood-brain barrier integrity by increasing cerebrovascular oxidative stress. *Biochemical and biophysical research communications*. 2014 Mar 7;445(2):352-6.
- [62] Vuletic S, Jin LW, Marcovina SM, Peskind ER, Moller T, Albers JJ. Widespread distribution of PLTP in human CNS: evidence for PLTP synthesis by glia and neurons, and increased levels in Alzheimer's disease. *Journal of lipid research*. 2003 Jun;44(6):1113-23.
- [63] Vuletic S, Peskind ER, Marcovina SM, Quinn JF, Cheung MC, Kennedy H, et al. Reduced CSF PLTP activity in Alzheimer's disease and other neurologic diseases; PLTP induces ApoE secretion in primary human astrocytes in vitro. *Journal of neuroscience research*. 2005 May 1;80(3):406-13.
- [64] Dong W, Albers JJ, Vuletic S. Phospholipid transfer protein reduces phosphorylation of tau in human neuronal cells. *Journal of neuroscience research*. 2009 Nov 1;87(14):3176-85.

- [65] Kingwell BA, Chapman MJ, Kontush A, Miller NE. HDL-targeted therapies: progress, failures and future. *Nature reviews Drug discovery*. 2014 Jun;13(6):445-64.
- [66] Albers JJ, Tollefson JH, Wolfbauer G, Albright RE, Jr. Cholesteryl ester transfer protein in human brain. *International journal of clinical & laboratory research*. 1992;21(3):264-6.
- [67] Pape ME, Rehberg EF, Marotti KR, Melchior GW. Molecular cloning, sequence, and expression of cynomolgus monkey cholesteryl ester transfer protein. Inverse correlation between hepatic cholesteryl ester transfer protein mRNA levels and plasma high density lipoprotein levels. *Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association*. 1991 Nov-Dec;11(6):1759-71.
- [68] Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nature reviews Neuroscience*. 2009 May;10(5):333-44.
- [69] Holtzman DM, Herz J, Bu G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. *Cold Spring Harbor perspectives in medicine*. 2012 Mar;2(3):a006312.
- [70] Fryer JD, Demattos RB, McCormick LM, O'Dell MA, Spinner ML, Bales KR, 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. *The Journal of biological chemistry*. 2005 Jul 8;280(27):25754-9.
- [71] Kim J, Castellano JM, Jiang H, Basak JM, Parsadanian M, Pham V, et al. Overexpression of low-density lipoprotein receptor in the brain markedly inhibits amyloid deposition and increases extracellular A beta clearance. *Neuron*. 2009 Dec 10;64(5):632-44.
- [72] Liu Q, Zerbinatti CV, Zhang J, Hoe HS, Wang B, Cole SL, et al. Amyloid precursor protein regulates brain apolipoprotein E and cholesterol metabolism through lipoprotein receptor LRP1. *Neuron*. 2007 Oct 4;56(1):66-78.
- [73] Zerbinatti CV, Wahrle SE, Kim H, Cam JA, Bales K, Paul SM, et al. Apolipoprotein E and low density lipoprotein receptor-related protein facilitate intraneuronal Abeta42 accumulation in amyloid model mice. *The Journal of biological chemistry*. 2006 Nov 24;281(47):36180-6.
- [74] Lane-Donovan C, Philips GT, Herz J. More than Cholesterol Transporters: Lipoprotein Receptors in CNS Function and Neurodegeneration. *Neuron*. 2014 Aug 20;83(4):771-87.
- [75] Rice DS, Curran T. Role of the reelin signaling pathway in central nervous system development. *Annual review of neuroscience*. 2001;24:1005-39.
- [76] Herz J, Chen Y. Reelin, lipoprotein receptors and synaptic plasticity. *Nature reviews Neuroscience*. 2006 Nov;7(11):850-9.

- [77] Leeb C, Eresheim C, Nimpf J. Clusterin is a ligand for apolipoprotein E receptor 2 (ApoER2) and very low density lipoprotein receptor (VLDLR) and signals via the Reelin- signaling pathway. *The Journal of biological chemistry*. 2014 Feb 14;289(7):4161-72.
- [78] Christie RH, Chung H, Rebeck GW, Strickland D, Hyman BT. Expression of the very low-density lipoprotein receptor (VLDL-r), an apolipoprotein-E receptor, in the central nervous system and in Alzheimer's disease. *Journal of neuropathology and experimental neurology*. 1996 Apr;55(4):491-8.
- [79] Clatworthy AE, Stockinger W, Christie RH, Schneider WJ, Nimpf J, Hyman BT, et al. Expression and alternate splicing of apolipoprotein E receptor 2 in brain. *Neuroscience*. 1999 Mar;90(3):903-11.
- [80] Moestrup SK, Gliemann J, Pallesen G. Distribution of the alpha 2-macroglobulin receptor/low density lipoprotein receptor-related protein in human tissues. *Cell and tissue research*. 1992 Sep;269(3):375-82.
- [81] Rapp A, Gmeiner B, Huttinger M. Implication of apoE isoforms in cholesterol metabolism by primary rat hippocampal neurons and astrocytes. *Biochimie*. 2006 May;88(5):473-83.
- [82] Rebeck GW, LaDu MJ, Estus S, Bu G, Weeber EJ. The generation and function of soluble apoE receptors in the CNS. *Molecular neurodegeneration*. 2006;1:15.
- [83] Spuch C, Ortolano S, Navarro C. LRP-1 and LRP-2 receptors function in the membrane neuron. Trafficking mechanisms and proteolytic processing in Alzheimer's disease. *Frontiers in physiology*. 2012;3:269.
- [84] Motoi Y, Aizawa T, Haga S, Nakamura S, Namba Y, Ikeda K. Neuronal localization of a novel mosaic apolipoprotein E receptor, LR11, in rat and human brain. *Brain research*. 1999 Jul 3;833(2):209-15.
- [85] Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2012 Jan;8(1):1-13.
- [86] Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature reviews Neuroscience*. 2011 Dec;12(12):723-38.
- [87] de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke; a journal of cerebral circulation*. 2002 Apr;33(4):1152-62.
- [88] Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. *Stroke; a journal of cerebral circulation*. 2004 Nov;35(11 Suppl 1):2620-2.
- [89] Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the

Cache County study. Alzheimer disease and associated disorders. 2006 Apr-Jun; 20(2):93-100.

- [90] Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. *Neurobiology of aging*. 2000 Mar-Apr;21(2):321-30.
- [91] Esiri MM, Nagy Z, Smith MZ, Barnettson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet*. 1999 Sep 11;354(9182):919-20.
- [92] Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, et al. AD lesions and infarcts in demented and non-demented Japanese-American men. *Annals of neurology*. 2005 Jan;57(1):98-103.
- [93] Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *Jama*. 1997 Mar 12;277(10):813-7.
- [94] Honjo K, van Reekum R, Verhoeff NP. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2009 Jul;5(4):348-60.
- [95] Kalaria RN, Bhatti SU, Lust WD, Perry G. The amyloid precursor protein in ischemic brain injury and chronic hypoperfusion. *Annals of the New York Academy of Sciences*. 1993 Sep 24;695:190-3.
- [96] Nihashi T, Inao S, Kajita Y, Kawai T, Sugimoto T, Niwa M, et al. Expression and distribution of beta amyloid precursor protein and beta amyloid peptide in reactive astrocytes after transient middle cerebral artery occlusion. *Acta neurochirurgica*. 2001;143(3):287-95.
- [97] Takeda S, Sato N, Morishita R. Systemic inflammation, blood-brain barrier vulnerability and cognitive/non-cognitive symptoms in Alzheimer disease: relevance to pathogenesis and therapy. *Frontiers in aging neuroscience*. 2014;6:171.
- [98] Foley P. Lipids in Alzheimer's disease: A century-old story. *Biochimica et biophysica acta*. 2010 Aug;1801(8):750-3.
- [99] Di Paolo G, Kim TW. Linking lipids to Alzheimer's disease: cholesterol and beyond. *Nature reviews Neuroscience*. 2011 May;12(5):284-96.
- [100] Kosicek M, Hecimovic S. Phospholipids and Alzheimer's disease: alterations, mechanisms and potential biomarkers. *International journal of molecular sciences*. 2013;14(1):1310-22.
- [101] Han X, Fagan AM, Cheng H, Morris JC, Xiong C, Holtzman DM. Cerebrospinal fluid sulfatide is decreased in subjects with incipient dementia. *Annals of neurology*. 2003 Jul;54(1):115-9.

- [102] Satoi H, Tomimoto H, Ohtani R, Kitano T, Kondo T, Watanabe M, et al. Astroglial expression of ceramide in Alzheimer's disease brains: a role during neuronal apoptosis. *Neuroscience*. 2005;130(3):657-66.
- [103] Soderberg M, Edlund C, Kristensson K, Dallner G. Fatty acid composition of brain phospholipids in aging and in Alzheimer's disease. *Lipids*. 1991 Jun;26(6):421-5.
- [104] Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. *The British journal of nutrition*. 2003 Apr;89(4):483-9.
- [105] Bennett SA, Valenzuela N, Xu H, Franko B, Fai S, Figeys D. Using neurolipidomics to identify phospholipid mediators of synaptic (dys)function in Alzheimer's Disease. *Frontiers in physiology*. 2013;4:168.
- [106] Estus S, Golde TE, Younkin SG. Normal processing of the Alzheimer's disease amyloid beta protein precursor generates potentially amyloidogenic carboxyl-terminal derivatives. *Annals of the New York Academy of Sciences*. 1992 Dec 31;674:138-48.
- [107] Haass C, Selkoe DJ. Cellular processing of beta-amyloid precursor protein and the genesis of amyloid beta-peptide. *Cell*. 1993 Dec 17;75(6):1039-42.
- [108] Seubert P, Vigo-Pelfrey C, Esch F, Lee M, Dovey H, Davis D, et al. Isolation and quantification of soluble Alzheimer's beta-peptide from biological fluids. *Nature*. 1992 Sep 24;359(6393):325-7.
- [109] Masters CL, Selkoe DJ. Biochemistry of amyloid beta-protein and amyloid deposits in Alzheimer disease. *Cold Spring Harbor perspectives in medicine*. 2012 Jun;2(6):a006262.
- [110] Haass C, Kaether C, Thinakaran G, Sisodia S. Trafficking and proteolytic processing of APP. *Cold Spring Harbor perspectives in medicine*. 2012 May;2(5):a006270.
- [111] Grziwa B, Grimm MO, Masters CL, Beyreuther K, Hartmann T, Lichtenthaler SF. The transmembrane domain of the amyloid precursor protein in microsomal membranes is on both sides shorter than predicted. *The Journal of biological chemistry*. 2003 Feb 28;278(9):6803-8.
- [112] Vetrivel KS, Thinakaran G. Membrane rafts in Alzheimer's disease beta-amyloid production. *Biochimica et biophysica acta*. 2010 Aug;1801(8):860-7.
- [113] Grimm MO, Grimm HS, Patzold AJ, Zinser EG, Halonen R, Duering M, et al. Regulation of cholesterol and sphingomyelin metabolism by amyloid-beta and presenilin. *Nature cell biology*. 2005 Nov;7(11):1118-23.
- [114] Sawamura N, Ko M, Yu W, Zou K, Hanada K, Suzuki T, et al. Modulation of amyloid precursor protein cleavage by cellular sphingolipids. *The Journal of biological chemistry*. 2004 Mar 19;279(12):11984-91.

- [115] Puglielli L, Ellis BC, Saunders AJ, Kovacs DM. Ceramide stabilizes beta-site amyloid precursor protein-cleaving enzyme 1 and promotes amyloid beta-peptide biogenesis. *The Journal of biological chemistry*. 2003 May 30;278(22):19777-83.
- [116] Haass C, Schlossmacher MG, Hung AY, Vigo-Pelfrey C, Mellon A, Ostaszewski BL, et al. Amyloid beta-peptide is produced by cultured cells during normal metabolism. *Nature*. 1992 Sep 24;359(6393):322-5.
- [117] Shoji M, Golde TE, Ghiso J, Cheung TT, Estus S, Shaffer LM, et al. Production of the Alzheimer amyloid beta protein by normal proteolytic processing. *Science*. 1992 Oct 2;258(5079):126-9.
- [118] Tanzi RE. The genetics of Alzheimer disease. *Cold Spring Harbor perspectives in medicine*. 2012 Oct;2(10).
- [119] Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, et al. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science*. 2010 Dec 24;330(6012):1774.
- [120] Kanekiyo T, Xu H, Bu G. ApoE and Abeta in Alzheimer's disease: accidental encounters or partners? *Neuron*. 2014 Feb 19;81(4):740-54.
- [121] Tanzi RE, Moir RD, Wagner SL. Clearance of Alzheimer's Abeta peptide: the many roads to perdition. *Neuron*. 2004 Sep 2;43(5):605-8.
- [122] Wildsmith KR, Holley M, Savage JC, Skerrett R, Landreth GE. Evidence for impaired amyloid beta clearance in Alzheimer's disease. *Alzheimer's research & therapy*. 2013;5(4):33.
- [123] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993 Aug 13;261(5123):921-3.
- [124] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, 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. *Jama*. 1997 Oct 22-29;278(16):1349-56.
- [125] Ward A, Crean S, Mercaldi CJ, Collins JM, Boyd D, Cook MN, et al. Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/e4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology*. 2012;38(1):1-17.
- [126] Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. *Neuron*. 1993 Oct;11(4):575-80.
- [127] Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-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. 1993 Mar 1;90(5):1977-81.
- [128] Verghese PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet neurology*. 2011 Mar;10(3):241-52.
 - [129] Garai K, Verghese PB, Baban B, Holtzman DM, Frieden C. The Binding of Apolipoprotein E to Oligomers and Fibrils of Amyloid-beta Alters the Kinetics of Amyloid Aggregation. *Biochemistry*. 2014 Sep 25.
 - [130] Zlokovic BV. Cerebrovascular effects of apolipoprotein E: implications for Alzheimer disease. *JAMA neurology*. 2013 Apr;70(4):440-4.
 - [131] Chalmers K, Wilcock GK, Love S. APOE epsilon 4 influences the pathological phenotype of Alzheimer's disease by favouring cerebrovascular over parenchymal accumulation of A beta protein. *Neuropathology and applied neurobiology*. 2003 Jun;29(3):231-8.
 - [132] Premkumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN. Apolipoprotein E-epsilon4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. *The American journal of pathology*. 1996 Jun;148(6):2083-95.
 - [133] Mak AC, Pullinger CR, Tang LF, Wong JS, Deo RC, Schwarz JM, et al. Effects of the Absence of Apolipoprotein E on Lipoproteins, Neurocognitive Function, and Retinal Function. *JAMA neurology*. 2014 Aug 11.
 - [134] Bales KR, Verina T, Cummins DJ, Du Y, Dodel RC, Saura J, et al. Apolipoprotein E is essential for amyloid deposition in the APP(V717F) transgenic mouse model of Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*. 1999 Dec 21;96(26):15233-8.
 - [135] Kim J, Jiang H, Park S, Eltorai AE, Stewart FR, Yoon H, et al. Haploinsufficiency of human APOE reduces amyloid deposition in a mouse model of amyloid-beta amyloidosis. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011 Dec 7;31(49):18007-12.
 - [136] Bien-Ly N, Gillespie AK, Walker D, Yoon SY, Huang Y. Reducing human apolipoprotein E levels attenuates age-dependent Abeta accumulation in mutant human amyloid precursor protein transgenic mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2012 Apr 4;32(14):4803-11.
 - [137] Holtzman DM, Fagan AM, Mackey B, Tenkova T, Sartorius L, Paul SM, et al. Apolipoprotein E facilitates neuritic and cerebrovascular plaque formation in an Alzheimer's disease model. *Annals of neurology*. 2000 Jun;47(6):739-47.
 - [138] Geschwind DH. Tau phosphorylation, tangles, and neurodegeneration: the chicken or the egg? *Neuron*. 2003 Oct 30;40(3):457-60.

- [139] Brecht WJ, Harris FM, Chang S, Tesseur I, Yu GQ, Xu Q, et al. Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2004 Mar 10;24(10):2527-34.
- [140] Mahley RW, Huang Y. Apolipoprotein e sets the stage: response to injury triggers neuropathology. *Neuron*. 2012 Dec 6;76(5):871-85.
- [141] Hamanaka H, Katoh-Fukui Y, Suzuki K, Kobayashi M, Suzuki R, Motegi Y, et al. Altered cholesterol metabolism in human apolipoprotein E4 knock-in mice. *Human molecular genetics*. 2000 Feb 12;9(3):353-61.
- [142] Klein RC, Mace BE, Moore SD, Sullivan PM. Progressive loss of synaptic integrity in human apolipoprotein E4 targeted replacement mice and attenuation by apolipoprotein E2. *Neuroscience*. 2010 Dec 29;171(4):1265-72.
- [143] Chen Y, Durakoglugil MS, Xian X, Herz J. ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling. *Proceedings of the National Academy of Sciences of the United States of America*. 2010 Jun 29;107(26):12011-6.
- [144] Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Über eine eigenartige Erkrankung der Hirnrinde". *Clinical anatomy*. 1995;8(6):429-31.
- [145] LaDu MJ, Shah JA, Reardon CA, Getz GS, Bu G, Hu J, et al. Apolipoprotein E and apolipoprotein E receptors modulate A beta-induced glial neuroinflammatory responses. *Neurochemistry international*. 2001 Nov-Dec;39(5-6):427-34.
- [146] Pocivavsek A, Mikhailenko I, Strickland DK, Rebeck GW. Microglial low-density lipoprotein receptor-related protein 1 modulates c-Jun N-terminal kinase activation. *Journal of neuroimmunology*. 2009 Sep 29;214(1-2):25-32.
- [147] Keene CD, Cudaback E, Li X, Montine KS, Montine TJ. Apolipoprotein E isoforms and regulation of the innate immune response in brain of patients with Alzheimer's disease. *Current opinion in neurobiology*. 2011 Dec;21(6):920-8.
- [148] Grainger DJ, Reckless J, McKilligin E. Apolipoprotein E modulates clearance of apoptotic bodies in vitro and in vivo, resulting in a systemic proinflammatory state in apolipoprotein E-deficient mice. *Journal of immunology*. 2004 Nov 15;173(10):6366-75.
- [149] Lynch JR, Tang W, Wang H, Vitek MP, Bennett ER, Sullivan PM, et al. APOE genotype and an ApoE-mimetic peptide modify the systemic and central nervous system inflammatory response. *The Journal of biological chemistry*. 2003 Dec 5;278(49):48529-33.

- [150] Rodriguez GA, Tai LM, LaDu MJ, Rebeck GW. Human APOE4 increases microglia reactivity at Abeta plaques in a mouse model of Abeta deposition. *Journal of neuro-inflammation*. 2014;11:111.
- [151] Zhu Y, Nwabuisi-Heath E, Dumanis SB, Tai LM, Yu C, Rebeck GW, et al. APOE genotype alters glial activation and loss of synaptic markers in mice. *Glia*. 2012 Apr; 60(4):559-69.
- [152] Szekely CA, Breitner JC, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, et al. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. *Neurology*. 2008 Jan 1;70(1):17-24.
- [153] Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nature genetics*. 2009 Oct;41(10):1088-93.
- [154] Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nature genetics*. 2009 Oct;41(10):1094-9.
- [155] Jun G, Naj AC, Beecham GW, Wang LS, Buross J, Gallins PJ, et al. Meta-analysis confirms CR1, CLU, and PICALM as alzheimer disease risk loci and reveals interactions with APOE genotypes. *Archives of neurology*. 2010 Dec;67(12):1473-84.
- [156] Mullan GM, McEneny J, Fuchs M, McMaster C, Todd S, McGuinness B, et al. Plasma clusterin levels and the rs11136000 genotype in individuals with mild cognitive impairment and Alzheimer's disease. *Current Alzheimer research*. 2013 Nov;10(9): 973-8.
- [157] Thambisetty M, Simmons A, Velayudhan L, Hye A, Campbell J, Zhang Y, et al. Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. *Archives of general psychiatry*. 2010 Jul;67(7):739-48.
- [158] Schurmann B, Wiese B, Bickel H, Weyerer S, Riedel-Heller SG, Pentzek M, et al. Association of the Alzheimer's disease clusterin risk allele with plasma clusterin concentration. *Journal of Alzheimer's disease : JAD*. 2011;25(3):421-4.
- [159] Braskie MN, Jahanshad N, Stein JL, Barysheva M, McMahon KL, de Zubicaray GI, et al. Common Alzheimer's disease risk variant within the CLU gene affects white matter microstructure in young adults. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011 May 4;31(18):6764-70.
- [160] Erk S, Meyer-Lindenberg A, Opitz von Boberfeld C, Esslinger C, Schnell K, Kirsch P, et al. Hippocampal function in healthy carriers of the CLU Alzheimer's disease risk variant. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011 Dec 7;31(49):18180-4.
- [161] Lancaster TM, Baird A, Wolf C, Jackson MC, Johnston SJ, Donev R, et al. Neural hyperactivation in carriers of the Alzheimer's risk variant on the clusterin gene. *Europe-*

an neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2011 Dec;21(12):880-4.

- [162] Roussotte FF, Gutman BA, Madsen SK, Colby JB, Thompson PM, Alzheimer's Disease Neuroimaging I. Combined effects of Alzheimer risk variants in the CLU and ApoE genes on ventricular expansion patterns in the elderly. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2014 May 7;34(19):6537-45.
- [163] Thambisetty M, Beason-Held LL, An Y, Kraut M, Nalls M, Hernandez DG, et al. Alzheimer risk variant CLU and brain function during aging. *Biological psychiatry*. 2013 Mar 1;73(5):399-405.
- [164] Rodriguez-Rodriguez E, Sanchez-Juan P, Vazquez-Higuera JL, Mateo I, Pozueta A, Berciano J, et al. Genetic risk score predicting accelerated progression from mild cognitive impairment to Alzheimer's disease. *Journal of neural transmission*. 2013 May; 120(5):807-12.
- [165] Elias-Sonnenschein LS, Helisalmi S, Natunen T, Hall A, Paajanen T, Herukka SK, et al. Genetic loci associated with Alzheimer's disease and cerebrospinal fluid biomarkers in a Finnish case-control cohort. *PloS one*. 2013;8(4):e59676.
- [166] Kauwe JS, Cruchaga C, Karch CM, Sadler B, Lee M, Mayo K, et al. Fine mapping of genetic variants in BIN1, CLU, CR1 and PICALM for association with cerebrospinal fluid biomarkers for Alzheimer's disease. *PloS one*. 2011;6(2):e15918.
- [167] Jongbloed W, Herrebout MA, Blankenstein MA, Veerhuis R. Quantification of clusterin in paired cerebrospinal fluid and plasma samples. *Annals of clinical biochemistry*. 2014 Sep;51(Pt 5):557-67.
- [168] Desikan RS, Thompson WK, Holland D, Hess CP, Brewer JB, Zetterberg H, et al. The role of clusterin in amyloid-beta-associated neurodegeneration. *JAMA neurology*. 2014 Feb;71(2):180-7.
- [169] Harr SD, Uint L, Hollister R, Hyman BT, Mendez AJ. Brain expression of apolipoproteins E, J, and A-I in Alzheimer's disease. *Journal of neurochemistry*. 1996 Jun;66(6):2429-35.
- [170] Nilselid AM, Davidsson P, Nagga K, Andreasen N, Fredman P, Blennow K. Clusterin in cerebrospinal fluid: analysis of carbohydrates and quantification of native and glycosylated forms. *Neurochemistry international*. 2006 Jun;48(8):718-28.
- [171] Sihlbom C, Davidsson P, Sjogren M, Wahlund LO, Nilsson CL. Structural and quantitative comparison of cerebrospinal fluid glycoproteins in Alzheimer's disease patients and healthy individuals. *Neurochemical research*. 2008 Jul;33(7):1332-40.
- [172] Baig S, Palmer LE, Owen MJ, Williams J, Kehoe PG, Love S. Clusterin mRNA and protein in Alzheimer's disease. *Journal of Alzheimer's disease : JAD*. 2012;28(2):337-44.

- [173] May PC, Johnson SA, Poirier J, Lampert-Etchells M, Finch CE. Altered gene expression in Alzheimer's disease brain tissue. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques*. 1989 Nov;16(4 Suppl):473-6.
- [174] Bertrand P, Poirier J, Oda T, Finch CE, Pasinetti GM. Association of apolipoprotein E genotype with brain levels of apolipoprotein E and apolipoprotein J (clusterin) in Alzheimer disease. *Brain research Molecular brain research*. 1995 Oct;33(1):174-8.
- [175] Chen LH, Kao PY, Fan YH, Ho DT, Chan CS, Yik PY, et al. Polymorphisms of CR1, CLU and PICALM confer susceptibility of Alzheimer's disease in a southern Chinese population. *Neurobiology of aging*. 2012 Jan;33(1):210 e1-7.
- [176] Lidstrom AM, Bogdanovic N, Hesse C, Volkman I, Davidsson P, Blennow K. Clusterin (apolipoprotein J) protein levels are increased in hippocampus and in frontal cortex in Alzheimer's disease. *Experimental neurology*. 1998 Dec;154(2):511-21.
- [177] Oda T, Pasinetti GM, Osterburg HH, Anderson C, Johnson SA, Finch CE. Purification and characterization of brain clusterin. *Biochemical and biophysical research communications*. 1994 Nov 15;204(3):1131-6.
- [178] Martin-Rehrmann MD, Hoe HS, Capuani EM, Rebeck GW. Association of apolipoprotein J-positive beta-amyloid plaques with dystrophic neurites in Alzheimer's disease brain. *Neurotoxicity research*. 2005;7(3):231-42.
- [179] McGeer PL, Kawamata T, Walker DG. Distribution of clusterin in Alzheimer brain tissue. *Brain research*. 1992 May 8;579(2):337-41.
- [180] Howlett DR, Hortobagyi T, Francis PT. Clusterin associates specifically with Abeta40 in Alzheimer's disease brain tissue. *Brain pathology*. 2013 Nov;23(6):623-32.
- [181] Kida S, Weller RO, Zhang ET, Phillips MJ, Iannotti F. Anatomical pathways for lymphatic drainage of the brain and their pathological significance. *Neuropathology and applied neurobiology*. 1995 Jun;21(3):181-4.
- [182] Hughes TM, Lopez OL, Evans RW, Kamboh MI, Williamson JD, Klunk WE, et al. Markers of cholesterol transport are associated with amyloid deposition in the brain. *Neurobiology of aging*. 2014 Apr;35(4):802-7.
- [183] Silajdzic E, Minthon L, Bjorkqvist M, Hansson O. No diagnostic value of plasma clusterin in Alzheimer's disease. *PloS one*. 2012;7(11):e50237.
- [184] Thambisetty M, An Y, Kinsey A, Koka D, Saleem M, Guntert A, et al. Plasma clusterin concentration is associated with longitudinal brain atrophy in mild cognitive impairment. *NeuroImage*. 2012 Jan 2;59(1):212-7.
- [185] L IJ, Dekker LJ, Koudstaal PJ, Hofman A, Sillevius Smitt PA, Breteler MM, et al. Serum clusterin levels are not increased in presymptomatic Alzheimer's disease. *Journal of proteome research*. 2011 Apr 1;10(4):2006-10.

- [186] Hye A, Riddoch-Contreras J, Baird AL, Ashton NJ, Bazenet C, Leung R, et al. Plasma proteins predict conversion to dementia from prodromal disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2014 Jul 3.
- [187] Schrijvers EM, Koudstaal PJ, Hofman A, Breteler MM. Plasma clusterin and the risk of Alzheimer disease. *Jama*. 2011 Apr 6;305(13):1322-6.
- [188] Thambisetty M. Do extracellular chaperone proteins in plasma have potential as Alzheimer's disease biomarkers? *Biomarkers in medicine*. 2010 Dec;4(6):831-4.
- [189] DeMattos RB, O'Dell M A, Parsadanian M, Taylor JW, Harmony JA, Bales KR, et al. Clusterin promotes amyloid plaque formation and is critical for neuritic toxicity in a mouse model of Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2002 Aug 6;99(16):10843-8.
- [190] Mulder SD, Nielsen HM, Blankenstein MA, Eikelenboom P, Veerhuis R. Apolipoproteins E and J interfere with amyloid-beta uptake by primary human astrocytes and microglia in vitro. *Glia*. 2014 Apr;62(4):493-503.
- [191] Killick R, Ribe EM, Al-Shawi R, Malik B, Hooper C, Fernandes C, et al. Clusterin regulates beta-amyloid toxicity via Dickkopf-1-driven induction of the wnt-PCP-JNK pathway. *Molecular psychiatry*. 2014 Jan;19(1):88-98.
- [192] Bell RD, Sagare AP, Friedman AE, Bedi GS, Holtzman DM, Deane R, et al. Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse central nervous system. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2007 May;27(5):909-18.
- [193] Narayan P, Meehan S, Carver JA, Wilson MR, Dobson CM, Klenerman D. Amyloid-beta oligomers are sequestered by both intracellular and extracellular chaperones. *Biochemistry*. 2012 Nov 20;51(46):9270-6.
- [194] Saczynski JS, White L, Peila RL, Rodriguez BL, Launer LJ. The relation between apolipoprotein A-I and dementia: the Honolulu-Asia aging study. *American journal of epidemiology*. 2007 May 1;165(9):985-92.
- [195] Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. *Archives of neurology*. 2010 Dec;67(12):1491-7.
- [196] Reed B, Villeneuve S, Mack W, DeCarli C, Chui HC, Jagust W. Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA neurology*. 2014 Feb;71(2):195- 200.
- [197] Kawano M, Kawakami M, Otsuka M, Yashima H, Yaginuma T, Ueki A. Marked decrease of plasma apolipoprotein AI and AII in Japanese patients with late-onset non-familial Alzheimer's disease. *Clinica chimica acta; international journal of clinical chemistry*. 1995 Aug 14;239(2):209-11.

- [198] Kuriyama M, Takahashi K, Yamano T, Hokezu Y, Togo S, Osame M, et al. Low levels of serum apolipoprotein A I and A II in senile dementia. *The Japanese journal of psychiatry and neurology*. 1994 Sep;48(3):589-93.
- [199] Shih YH, Tsai KJ, Lee CW, Shiesh SC, Chen WT, Pai MC, et al. Apolipoprotein C-III is an Amyloid-beta-Binding Protein and an Early Marker for Alzheimer's Disease. *Journal of Alzheimer's disease : JAD*. 2014 Mar 31.
- [200] Merched A, Xia Y, Visvikis S, Serot JM, Siest G. Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease. *Neurobiology of aging*. 2000 Jan-Feb;21(1):27-30.
- [201] Castano EM, Roher AE, Esh CL, Kokjohn TA, Beach T. Comparative proteomics of cerebrospinal fluid in neuropathologically-confirmed Alzheimer's disease and non-demented elderly subjects. *Neurological research*. 2006 Mar;28(2):155-63.
- [202] Song H, Saito K, Seishima M, Noma A, Urakami K, Nakashima K. Cerebrospinal fluid apo E and apo A-I concentrations in early- and late-onset Alzheimer's disease. *Neuroscience letters*. 1997 Aug 15;231(3):175-8.
- [203] Lefterov I, Fitz NF, Cronican AA, Fogg A, Lefterov P, Kodali R, et al. Apolipoprotein A-I deficiency increases cerebral amyloid angiopathy and cognitive deficits in APP/PS1DeltaE9 mice. *The Journal of biological chemistry*. 2010 Nov 19;285(47):36945-57.
- [204] Lewis TL, Cao D, Lu H, Mans RA, Su YR, Jungbauer L, et al. Overexpression of human apolipoprotein A-I preserves cognitive function and attenuates neuroinflammation and cerebral amyloid angiopathy in a mouse model of Alzheimer disease. *The Journal of biological chemistry*. 2010 Nov 19;285(47):36958-68.
- [205] de Magalhaes JP, Curado J, Church GM. Meta-analysis of age-related gene expression profiles identifies common signatures of aging. *Bioinformatics*. 2009 Apr 1;25(7):875-81.
- [206] Terrisse L, Poirier J, Bertrand P, Merched A, Visvikis S, Siest G, et al. Increased levels of apolipoprotein D in cerebrospinal fluid and hippocampus of Alzheimer's patients. *Journal of neurochemistry*. 1998 Oct;71(4):1643-50.
- [207] Glockner F, Ohm TG. Hippocampal apolipoprotein D level depends on Braak stage and APOE genotype. *Neuroscience*. 2003;122(1):103-10.
- [208] Abildayeva K, Berbee JF, Blokland A, Jansen PJ, Hoek FJ, Meijer O, et al. Human apolipoprotein C-I expression in mice impairs learning and memory functions. *Journal of lipid research*. 2008 Apr;49(4):856-69.
- [209] Cudaback E, Li X, Yang Y, Yoo T, Montine KS, Craft S, et al. Apolipoprotein C-I is an APOE genotype-dependent suppressor of glial activation. *Journal of neuroinflammation*. 2012;9:192.

- [210] Poduslo SE, Neal M, Herring K, Shelly J. The apolipoprotein CI A allele as a risk factor for Alzheimer's disease. *Neurochemical research*. 1998 Mar;23(3):361-7.
- [211] Drigalenko E, Poduslo S, Elston R. Interaction of the apolipoprotein E and CI loci in predisposing to late-onset Alzheimer's disease. *Neurology*. 1998 Jul;51(1):131-5.
- [212] Csaszar A, Kalman J, Szalai C, Janka Z, Romics L. Association of the apolipoprotein A-IV codon 360 mutation in patients with Alzheimer's disease. *Neuroscience letters*. 1997 Jul 25;230(3):151-4.
- [213] Cui Y, Huang M, He Y, Zhang S, Luo Y. Genetic ablation of apolipoprotein A-IV accelerates Alzheimer's disease pathogenesis in a mouse model. *The American journal of pathology*. 2011 Mar;178(3):1298-308.
- [214] Shih YH, Tsai KJ, Lee CW, Shiesh SC, Chen WT, Pai MC, et al. Apolipoprotein C-III is an amyloid-beta-binding protein and an early marker for Alzheimer's disease. *Journal of Alzheimer's disease : JAD*. 2014;41(3):855-65.
- [215] Pahnke J, Langer O, Krohn M. Alzheimer's and ABC transporters - new opportunities for diagnostics and treatment. *Neurobiology of disease*. 2014 Apr 16.
- [216] Koldamova R, Fitz NF, Lefterov I. ATP-binding cassette transporter A1: From metabolism to neurodegeneration. *Neurobiology of disease*. 2014 May 17.
- [217] Hirsch-Reinshagen V, Maia LF, Burgess BL, Blain JF, Naus KE, McIsaac SA, et al. The absence of ABCA1 decreases soluble ApoE levels but does not diminish amyloid deposition in two murine models of Alzheimer disease. *The Journal of biological chemistry*. 2005 Dec 30;280(52):43243-56.
- [218] Wahrle SE, Jiang H, Parsadanian M, Hartman RE, Bales KR, Paul SM, et al. Deletion of Abca1 increases Abeta deposition in the PDAPP transgenic mouse model of Alzheimer disease. *The Journal of biological chemistry*. 2005 Dec 30;280(52):43236-42.
- [219] Koldamova R, Staufenbiel M, Lefterov I. Lack of ABCA1 considerably decreases brain ApoE level and increases amyloid deposition in APP23 mice. *The Journal of biological chemistry*. 2005 Dec 30;280(52):43224-35.
- [220] Lefterov I, Fitz NF, Cronican A, Lefterov P, Staufenbiel M, Koldamova R. Memory deficits in APP23/Abca1+/- mice correlate with the level of Abeta oligomers. *ASN neuro*. 2009;1(2).
- [221] Fitz NF, Cronican AA, Saleem M, Fauq AH, Chapman R, Lefterov I, et al. Abca1 deficiency affects Alzheimer's disease-like phenotype in human ApoE4 but not in ApoE3- targeted replacement mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2012 Sep 19;32(38):13125-36.
- [222] Lefterov I, Bookout A, Wang Z, Staufenbiel M, Mangelsdorf D, Koldamova R. Expression profiling in APP23 mouse brain: inhibition of Abeta amyloidosis and in-

flammation in response to LXR agonist treatment. *Molecular neurodegeneration*. 2007;2:20.

- [223] Koldamova RP, Lefterov IM, Staufenbiel M, Wolfe D, Huang S, Glorioso JC, et al. The liver X receptor ligand T0901317 decreases amyloid beta production in vitro and in a mouse model of Alzheimer's disease. *The Journal of biological chemistry*. 2005 Feb 11;280(6):4079-88.
- [224] Riddell DR, Zhou H, Comery TA, Kouranova E, Lo CF, Warwick HK, et al. The LXR agonist T0901317 selectively lowers hippocampal Abeta42 and improves memory in the Tg2576 mouse model of Alzheimer's disease. *Molecular and cellular neurosciences*. 2007 Apr;34(4):621-8.
- [225] Jiang Q, Lee CY, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, et al. ApoE promotes the proteolytic degradation of Abeta. *Neuron*. 2008 Jun 12;58(5):681-93.
- [226] Fitz NF, Cronican A, Pham T, Fogg A, Fauq AH, Chapman R, et al. Liver X receptor agonist treatment ameliorates amyloid pathology and memory deficits caused by high-fat diet in APP23 mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2010 May 19;30(20):6862-72.
- [227] Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo JC, Zinn AE, et al. ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. *Science*. 2012 Mar 23;335(6075):1503-6.
- [228] Vanmierlo T, Rutten K, Dederen J, Bloks VW, van Vark-van der Zee LC, Kuipers F, et al. Liver X receptor activation restores memory in aged AD mice without reducing amyloid. *Neurobiology of aging*. 2011 Jul;32(7):1262-72.
- [229] Donkin JJ, Stukas S, Hirsch-Reinshagen V, Namjoshi D, Wilkinson A, May S, et al. ATP-binding cassette transporter A1 mediates the beneficial effects of the liver X receptor agonist GW3965 on object recognition memory and amyloid burden in amyloid precursor protein/presenilin 1 mice. *The Journal of biological chemistry*. 2010 Oct 29;285(44):34144- 54.
- [230] Fitz NF, Castranio EL, Carter AY, Kodali R, Lefterov I, Koldamova R. Improvement of Memory Deficits and Amyloid-beta Clearance in Aged APP23 Mice Treated with a Combination of Anti-Amyloid-beta Antibody and LXR Agonist. *Journal of Alzheimer's disease: JAD*. 2014 Mar 18.
- [231] Fitz NF, Cronican AA, Lefterov I, Koldamova R. Comment on "ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models". *Science*. 2013 May 24;340(6135):924-c.
- [232] Tesseur I, Lo AC, Roberfroid A, Dietvorst S, Van Broeck B, Borgers M, et al. Comment on "ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models". *Science*. 2013 May 24;340(6135):924-e.

- [233] Wang XF, Cao YW, Feng ZZ, Fu D, Ma YS, Zhang F, et al. Quantitative assessment of the effect of ABCA1 gene polymorphism on the risk of Alzheimer's disease. *Molecular biology reports*. 2013 Feb;40(2):779-85.
- [234] Frikke-Schmidt R, Nordestgaard BG, Stene MC, Sethi AA, Remaley AT, Schnohr P, et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. *Jama*. 2008 Jun 4;299(21):2524-32.
- [235] Clee SM, Kastelein JJ, van Dam M, Marcil M, Roomp K, Zwarts KY, et al. Age and residual cholesterol efflux affect HDL cholesterol levels and coronary artery disease in ABCA1 heterozygotes. *The Journal of clinical investigation*. 2000 Nov;106(10):1263-70.
- [236] Rader DJ, deGoma EM. Approach to the patient with extremely low HDL-cholesterol. *The Journal of clinical endocrinology and metabolism*. 2012 Oct;97(10):3399-407.
- [237] Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buross J, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nature genetics*. 2011 May;43(5):436-41.
- [238] Allen M, Zou F, Chai HS, Younkin CS, Crook J, Pankratz VS, et al. Novel late-onset Alzheimer disease loci variants associate with brain gene expression. *Neurology*. 2012 Jul 17;79(3):221-8.
- [239] Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C, Goate AM. Expression of novel Alzheimer's disease risk genes in control and Alzheimer's disease brains. *PloS one*. 2012;7(11):e50976.
- [240] Reitz C, Jun G, Naj A, Rajbhandary R, Vardarajan BN, Wang LS, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4, and the risk of late-onset Alzheimer disease in African Americans. *Jama*. 2013 Apr 10;309(14):1483-92.
- [241] Vasquez JB, Fardo DW, Estus S. ABCA7 expression is associated with Alzheimer's disease polymorphism and disease status. *Neuroscience letters*. 2013 Nov 27;556:58-62.
- [242] Shulman JM, Chen K, Keenan BT, Chibnik LB, Fleisher A, Thiyyagura P, et al. Genetic susceptibility for Alzheimer disease neuritic plaque pathology. *JAMA neurology*. 2013 Sep 1;70(9):1150-7.
- [243] Beecham GW, Hamilton K, Naj AC, Martin ER, Huentelman M, Myers AJ, et al. Genome-Wide Association Meta-analysis of Neuropathologic Features of Alzheimer's Disease and Related Dementias. *PLoS genetics*. 2014 Sep;10(9):e1004606.
- [244] Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nature genetics*. 2011 May;43(5):429-35.

- [245] Kim WS, Li H, Ruberu K, Chan S, Elliott DA, Low JK, et al. Deletion of Abca7 increases cerebral amyloid-beta accumulation in the J20 mouse model of Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2013 Mar 6;33(10):4387-94.
- [246] Burgess BL, Parkinson PF, Racke MM, Hirsch-Reinshagen V, Fan J, Wong C, 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*. 2008 Jun;49(6):1254-67.
- [247] Rousset X, Shamburek R, Vaisman B, Amar M, Remaley AT. Lecithin cholesterol acyltransferase: an anti- or pro-atherogenic factor? *Current atherosclerosis reports*. 2011 Jun;13(3):249-56.
- [248] Desrumaux C, Pisoni A, Meunier J, Deckert V, Athias A, Perrier V, et al. Increased amyloid-beta peptide-induced memory deficits in phospholipid transfer protein (PLTP) gene knockout mice. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2013 Apr;38(5):817-25.
- [249] Wang H, Yu Y, Chen W, Cui Y, Luo T, Ma J, et al. PLTP deficiency impairs learning and memory capabilities partially due to alteration of amyloid-beta metabolism in old mice. *Journal of Alzheimer's disease : JAD*. 2014;39(1):79-88.
- [250] Arias-Vasquez A, Isaacs A, Aulchenko YS, Hofman A, Oostra BA, Breteler M, et al. The cholesteryl ester transfer protein (CETP) gene and the risk of Alzheimer's disease. *Neurogenetics*. 2007 Aug;8(3):189-93.
- [251] Barzilai N, Atzmon G, Schechter C, Schaefer EJ, Cupples AL, Lipton R, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. *Jama*. 2003 Oct 15;290(15):2030-40.
- [252] Cellini E, Nacmias B, Olivieri F, Ortenzi L, Tedde A, Bagnoli S, et al. Cholesteryl ester transfer protein (CETP) I405V polymorphism and longevity in Italian centenarians. *Mechanisms of ageing and development*. 2005 Jun-Jul;126(6-7):826-8.
- [253] Li Q, Huang P, He QC, Lin QZ, Wu J, Yin RX. Association between the CETP polymorphisms and the risk of Alzheimer's disease, carotid atherosclerosis, longevity, and the efficacy of statin therapy. *Neurobiology of aging*. 2014 Jun;35(6):1513 e13-23.
- [254] Novelli V, Viviani Anselmi C, Roncarati R, Guffanti G, Malovini A, Piluso G, et al. Lack of replication of genetic associations with human longevity. *Biogerontology*. 2008 Apr;9(2):85-92.
- [255] Sun L, Hu CY, Shi XH, Zheng CG, Huang ZZ, Lv ZP, et al. Trans-ethnic shift of the risk genotype in the CETP I405V with longevity: a Chinese case-control study and meta- analysis. *PloS one*. 2013;8(8):e72537.

- [256] Yang JK, Gong YY, Xie L, Yang Y, Xu LY, Zhang YP. Association study of promoter polymorphisms in the CETP gene with longevity in the Han Chinese population. *Molecular biology reports*. 2014 Jan;41(1):325-9.
- [257] Warstadt NM, Dennis EL, Jahanshad N, Kohannim O, Nir TM, McMahon KL, et al. Serum cholesterol and variant in cholesterol-related gene CETP predict white matter microstructure. *Neurobiology of aging*. 2014 Nov;35(11):2504-13.
- [258] Rodriguez E, Mateo I, Infante J, Llorca J, Berciano J, Combarros O. Cholesteryl ester transfer protein (CETP) polymorphism modifies the Alzheimer's disease risk associated with APOE epsilon4 allele. *Journal of neurology*. 2006 Feb;253(2):181-5.
- [259] Chen Y, Jia L, Wei C, Wang F, Lv H, Jia J. Association between polymorphisms in the apolipoprotein D gene and sporadic Alzheimer's disease. *Brain research*. 2008 Oct 3;1233:196-202.
- [260] Murphy EA, Roddey JC, McEvoy LK, Holland D, Hagler DJ, Jr., Dale AM, et al. CETP polymorphisms associate with brain structure, atrophy rate, and Alzheimer's disease risk in an APOE-dependent manner. *Brain imaging and behavior*. 2012 Mar; 6(1):16-26.
- [261] Sanders AE, Wang C, Katz M, Derby CA, Barzilai N, Ozelius L, et al. Association of a functional polymorphism in the cholesteryl ester transfer protein (CETP) gene with memory decline and incidence of dementia. *Jama*. 2010 Jan 13;303(2):150-8.
- [262] Deane R, Wu Z, Sagare A, Davis J, Du Yan S, Hamm K, et al. LRP/amyloid beta- peptide interaction mediates differential brain efflux of Abeta isoforms. *Neuron*. 2004 Aug 5;43(3):333-44.
- [263] Kanekiyo T, Cirrito JR, Liu CC, Shinohara M, Li J, Schuler DR, et al. Neuronal clearance of amyloid-beta by endocytic receptor LRP1. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2013 Dec 4;33(49):19276-83.
- [264] Shibata M, Yamada S, Kumar SR, Calero M, Bading J, Frangione B, et al. Clearance of Alzheimer's amyloid-ss(1-40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier. *The Journal of clinical investigation*. 2000 Dec;106(12): 1489-99.
- [265] Tamamizu-Kato S, Cohen JK, Drake CB, Kosaraju MG, Drury J, Narayanaswami V. Interaction with amyloid beta peptide compromises the lipid binding function of apolipoprotein E. *Biochemistry*. 2008 May 6;47(18):5225-34.
- [266] Van Uden E, Mallory M, Veinbergs I, Alford M, Rockenstein E, Masliah E. Increased extracellular amyloid deposition and neurodegeneration in human amyloid precursor protein transgenic mice deficient in receptor-associated protein. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2002 Nov 1;22(21): 9298-304.

- [267] Deane R, Sagare A, Hamm K, Parisi M, Lane S, Finn MB, et al. apoE isoform-specific disruption of amyloid beta peptide clearance from mouse brain. *The Journal of clinical investigation*. 2008 Dec;118(12):4002-13.
- [268] Cao D, Fukuchi K, Wan H, Kim H, Li L. Lack of LDL receptor aggravates learning deficits and amyloid deposits in Alzheimer transgenic mice. *Neurobiology of aging*. 2006 Nov;27(11):1632-43.
- [269] Castellano JM, Deane R, Gottesdiener AJ, Verghese PB, Stewart FR, West T, et al. Low-density lipoprotein receptor overexpression enhances the rate of brain-to-blood Abeta clearance in a mouse model of beta-amyloidosis. *Proceedings of the National Academy of Sciences of the United States of America*. 2012 Sep 18;109(38):15502-7.
- [270] Beffert U, Morfini G, Bock HH, Reyna H, Brady ST, Herz J. Reelin-mediated signaling locally regulates protein kinase B/Akt and glycogen synthase kinase 3beta. *The Journal of biological chemistry*. 2002 Dec 20;277(51):49958-64.
- [271] Ohkubo N, Lee YD, Morishima A, Terashima T, Kikkawa S, Tohyama M, et al. Apolipoprotein E and Reelin ligands modulate tau phosphorylation through an apolipoprotein E receptor/disabled-1/glycogen synthase kinase-3beta cascade. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 2003 Feb;17(2):295-7.
- [272] Ridker PM. LDL cholesterol: controversies and future therapeutic directions. *Lancet*. 2014 Aug 16;384(9943):607-17.
- [273] Beffert U, Arguin C, Poirier J. The polymorphism in exon 3 of the low density lipoprotein receptor-related protein gene is weakly associated with Alzheimer's disease. *Neuroscience letters*. 1999 Jan 4;259(1):29-32.
- [274] Sanchez-Guerra M, Combarros O, Infante J, Llorca J, Berciano J, Fontalba A, et al. Case-control study and meta-analysis of low density lipoprotein receptor-related protein gene exon 3 polymorphism in Alzheimer's disease. *Neuroscience letters*. 2001 Dec 4;316(1):17-20.
- [275] Vazquez-Higuera JL, Mateo I, Sanchez-Juan P, Rodriguez-Rodriguez E, Pozueta A, Infante J, et al. Genetic interaction between tau and the apolipoprotein E receptor LRP1 Increases Alzheimer's disease risk. *Dementia and geriatric cognitive disorders*. 2009;28(2):116-20.
- [276] Vargas T, Bullido MJ, Martinez-Garcia A, Antequera D, Clarimon J, Rosich-Estrago M, et al. A megalin polymorphism associated with promoter activity and Alzheimer's disease risk. *American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2010 Jun 5;153B(4):895-902.
- [277] Wang LL, Pan XL, Wang Y, Tang HD, Deng YL, Ren RJ, et al. A single nucleotide polymorphism in LRP2 is associated with susceptibility to Alzheimer's disease in the

Chinese population. *Clinica chimica acta; international journal of clinical chemistry*. 2011 Jan 30;412(3-4):268-70.

- [278] Miyashita A, Koike A, Jun G, Wang LS, Takahashi S, Matsubara E, et al. SORL1 is genetically associated with late-onset Alzheimer's disease in Japanese, Koreans and Caucasians. *PloS one*. 2013;8(4):e58618.
- [279] Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, et al. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nature genetics*. 2007 Feb;39(2):168-77.
- [280] Scherzer CR, Offe K, Gearing M, Rees HD, Fang G, Heilman CJ, et al. Loss of apolipoprotein E receptor LR11 in Alzheimer disease. *Archives of neurology*. 2004 Aug; 61(8):1200-5.
- [281] Felsky D, Szeszko P, Yu L, Honer WG, De Jager PL, Schneider JA, et al. The SORL1 gene and convergent neural risk for Alzheimer's disease across the human lifespan. *Molecular psychiatry*. 2013 Oct 29.

