HHS Public Access

Author manuscript

Curr Alzheimer Res. Author manuscript; available in PMC 2018 March 06.

Published in final edited form as:

Curr Alzheimer Res. 2016 ; 13(11): 1200–1207.

Alzheimer's Disease Genetic Risk Factor APOE-ε4 Also Affects Normal Brain Function

Amanda M. DiBattista[a], **Nicolette M. Heinsinger**[a], and **G. William Rebeck**[*,a]

[a]Department of Neuroscience, Georgetown University, Washington, DC, USA

Abstract

APOE-ε4 is the strongest genetic risk factor for Alzheimer's disease (AD), and is associated with an increase in the levels of amyloid deposition and an early age of onset. Recent data demonstrate that AD pathological changes occur decades before clinical symptoms, raising questions about the precise onset of the disease. Now a convergence of approaches in mice and humans has demonstrated that APOE-ε4 affects normal brain function even very early in life in the absence of gross AD pathological changes. Normal mice expressing APOE4 have task-specific spatial learning deficits, as well as reduced NMDAR-dependent signaling and structural changes to presynaptic and postsynaptic compartments in neurons, particularly in hippocampal regions. Young humans possessing APOE-ε4 are more adept than APOE-ε4 negative individuals at some behavioral tasks, and functional magnetic resonance imaging has shown that inheritance of APOE-ε4 has specific effects on medial temporal brain activities. These findings suggest that inheritance of APOE-ε4 causes life long changes to the brain that may be related to the late risk of AD. Several possible mechanisms of how APOE-ε4 could affect brain neurochemistry, structure, and function are reviewed.

Keywords

apolippoprotein E; risk factor; hippocampus; entorhinal cortex; dendritic spine; amyloid; targeted replacement mice; prevention

1. INTRODUCTION

The neuropathological processes of Alzheimer's disease (AD) occur up to twenty years before clinical symptoms of the disease. Analysis of brain amyloid imaging and cerebrospinal fluid (CSF) biomarkers demonstrate early deposition of amyloid in individuals with causative genetic mutations in the amyloid precursor protein (APP), presenilin 1 or presenilin 2 [1], as well as those with the APOE-ε4 genetic risk factor [2]. These findings raise the possibility of preventing clinical symptoms of AD after recognition that amyloid accumulation has occurred [3].

[*]Corresponding author: G. William Rebeck, New Research Building, WP-13, 3970 Reservoir Rd, NW, Washington, DC 20007, 202-687-1534, gwr2@georgetown.edu.

CONFLICT OF INTEREST

The authors report no financial conflicts of interest.

In addition, these findings highlight the idea that AD processes occur slowly and that the onset of disease may begin even before it is recognized by amyloid accumulation. Carriers of the presenilin 1 mutation show higher levels of CSF $A\beta_{42}$ in childhood, as well as functional and structural changes in the brain [4]. Young APOE-ε4 individuals (reviewed below) show medial temporal lobe changes well before ages of overt amyloid deposition. These early differences in brain structure and function may reflect processes that allow the earlier amyloid accumulation to occur. In this review, we will consider the data from mice and humans that APOE genotype has effects on brain structure and function in the absence of amyloid. These effects could help identify new biomarkers of AD risk, complementing existing biomarkers based on AD pathological processes.

2. APOE GENOTYPE EFFECTS ON ALZHEIMER'S DISEASE

The greatest genetic risk for late onset Alzheimer's disease is associated with alleles of the apolipoprotein E (APOE) gene. APOE encodes for three isoforms of a secreted 299 amino acid protein (apoE2, apoE3, apoE4) that differ in amino acid sequence at positions 112 and 158 [5]. With an allele frequency of 14%, APOE-ε4 is present in approximately 25% of the US population and associated with increased risk of Alzheimer's Disease [2]; APOE-ε2 is present in about 14% of US individuals and has protective effects [6]. APOE-ε4 individuals have an earlier average age of AD onset by 10–15 years per allele [2]. Most of the genetic effect on age of onset of AD is accounted for by inheritance of APOE alleles [7]. Inexpensive genome sequencing and genomic testing now allow individuals to easily know their APOE genotype and its implied AD risk early in life, although there remains no clear treatments to lower risk associated with APOE-ε4.

In addition to raising disease risk, the APOE-ε4 allele also exacerbates brain changes associated with AD, increasing amyloid deposition and dysfunction of the medial temporal lobe. The APOE-ε4 allele is associated with increased brain amyloid in mild cognitive impairment and the early [8; 9] and late stages of AD (defined in post-mortem APOE-ε4 AD brains [10–12] or pre-mortem PET amyloid imaging [13]). This association of APOE-ε4 allele with increased amyloid is also observed in animal models of AD [12; 14; 15]. Anatomically, APOE-ε4 is associated with decreased hippocampal volumes in AD patients [16], and cognitively, APOE-ε4 is associated with greater memory impairment in AD [17]. Thus, late in life, APOE genotype preferentially has effects on amyloid accumulation and medial temporal lobe dysfunction.

However, the effects of APOE genotype are not limited to effects on AD pathological processes late in life. Throughout life, the apoE protein is important in brain lipid homeostasis [18] and synapse formation [19]. Complete knock-out of APOE causes profound alterations in serum lipoprotein types and levels [20; 21], although it does not have a strong effect on cognition or brain structure [22]. In order to define the effects of APOE genotype on normal healthy brains, data need to be generated from brains in the absence of AD pathological changes. In mice, this means analyzing mouse models that have not been developed to study AD pathological changes (i.e., mice not transgenic for APP). Any cognitive differences based on APOE genotype would not be due to amyloid accumulation, but rather to the effects of APOE genotype on other processes. In humans, this means

analyzing behavior in individuals with negative amyloid PET scans, or in populations too young to contain amyloid-positive individuals (i.e., within the first few decades of life). Thus, normal healthy subjects are defined here as those that have not been clinically diagnosed with cognitive impairment and do not exhibit AD-like pathology.

3. APOE GENOTYPE EFFECTS ON THE NORMAL BRAIN

3.1 APOE genotype effects on normal brain function in mice

Several models have been created to define the effects of APOE in mice, including APOE knock-out animals [23; 24] and animals with APOE expressed as part of a human bacterial artificial chromosome [25]. However, the simplest model is one in which the human APOE alleles have replaced the murine APOE, known as APOE Targeted Replacement (APOE TR) mice [26], which have a normal expression pattern of apoE [27]. The specific effects of APOE4 in brain have been investigated by comparing APOE4 TR mice with APOE3 and APOE2 TR mice. APOE4 TR mice have no gross AD pathology, such as amyloid plaques and neurofibrillary tangles [28], although there is evidence of intraneuronal $A\beta_{42}$ and phospho-tau in hippocampal subfields [29]. Thus, APOE TR mice are a good *in vivo* model to study the effects of APOE alleles in the normal brain lacking classical AD pathological changes.

3.1.1 Effects of APOE genotype on mouse behavior—Given the interest in the effects of APOE on AD, studies have generally focused more on the effects of APOE genotype on hippocampal-based behaviors. APOE4 TR mice have deficits in spatial learning as measured by the Barnes Maze [30] and the Morris Water Maze [31], as well as retention deficits in other spatial memory and passive avoidance tasks [32]. Female APOE4 TR mice are more vulnerable to memory and behavioral deficits than the male mice [32–35]. These studies support the conclusion that APOE4 TR mice have relatively subtle but measurable impairments in behavior dependent on the hippocampus.

3.1.2 Effects of APOE genotype on mouse brain structure—Neuronal structure has been investigated in APOE TR mice with biocytin filling of neurons, Golgi staining, and immunohistochemistry. These studies have revealed that neurons from young APOE4 TR mice (one to seven months of age) have simpler structures compared to APOE3 TR mice in the amygdala [28], cortical layers II/III [36], and the entorhinal cortex [30], including less dendritic branching, reduced spine density, and shorter dendritic spines. In older mice (16 months), APOE4 TR mice have fewer inhibitory neurons in the hippocampal hilus [37]. The reduced neuronal complexity may be related to spatial learning and memory impairments compared to APOE2 and APOE3 TR mice (section 3.1.1). Together, these data show that APOE4 is associated with gross changes to neuronal morphology throughout the brain.

3.1.3 Effects of APOE genotype on mouse brain function—The behavioral and structural differences observed in APOE4 TR mice also have molecular and biochemical correlates in the brain. Post-synaptically, middle-aged APOE4 TR mice have reduced spontaneous excitatory postsynaptic currents in the amygdala [28], but increased excitatory activity at old age [38]. APOE TR mice show alterations in long-term potentiation (LTP) in

different subregions of the hippocampus related to the NMDA glutamate receptor (NMDAR)-dependent signaling pathway: APOE4 TR mice show increased LTP in the mossy fibers compared to APOE2 TR mice [39], while APOE4 TR and APOE2 TR mice have reduced LTP compared to APOE3 TR mice in the dentate gyrus [40]. In addition, the hippocampi of the APOE4 TR mice show an increase in NMDAR-related signaling [39] and an age dependent difference in levels of a phosphorylated NMDAR subunit [41]. This latter effect may be due to differences in levels of the apoE receptor LRP1 [41].

Studies also demonstrate pre-synaptic differences based on APOE genotype. Compared to APOE2 and APOE3 TR mice, APOE4 TR mice have altered levels of the vesicular glutamate transporter, VGLUT1 [29; 42]. These effects are related to the diet of the animals, such that a diet high in fat results in APOE4 TR mice with lowered VGLUT1 levels [29; 43], while APOE4 TR mice fed a normal diet have increased VGLUT1 levels [42]. Since apoE is a lipid transporter, fat content in the diet may alter the pathological effects of APOE4 [43]. APOE4 TR mice also have increased brain glutamine levels and decreased levels of glutaminase, the enzyme responsible for the conversion of glutamine to glutamate [42]. Interestingly, several of the pre-synaptic differences observed are related to the glutamate cycle, suggesting that APOE4 may be disrupting the normal cycling of glutamate prior to AD onset [44].

Together, the studies of APOE4 TR mice show that, at an early age, APOE4 is associated with an altered brain biochemistry, reduced dendritic spine density, and deficits in behavior related to hippocampal functions.

3.2 APOE genotype effects on normal brain function in humans

Although the APOE knock-in mice allow easy analysis of brains homozygous for specific APOE alleles, human studies of the effects of APOE genotype have relied mostly on APOE-ε4 heterozygotes. While APOE-ε4/ε4 homozygotes are common in AD populations (approximately one tenth of AD patients in research studies [45]), they comprise less than two percent of control populations [46]. APOE-ε3/ε3 homozygotes comprise 50–75% of control populations [46], and are commonly used as a control sample.

3.2.1 Effects of APOE genotype on human behavior—There have been few studies on the effects of APOE genotype on behavior in humans ([47–50], with somewhat inconsistent results, perhaps due to confounding effects of age and sex. APOE genotype has no effect on measures of intelligence [51–54], or ability to perform Memory Island, mental rotation, and spatial span tasks [50]. However, for some measures, APOE-ε4 is associated with behavioral deficits: APOE-ε4-positive children have poorer immediate and delayed recall on the Family Pictures test and worse spatial memory retention on the Memory Island test, when sex is taken into account [47]. In several behavioral tasks, APOE-ε4 confers an advantage: college-aged APOE-ε4 carriers perform better in executive attention, verbal fluency, and memory tasks [55–58]. This positive effect at a young age of a characteristic that is detrimental in old age is known as an antagonistic pleiotropy hypothesis [58; 59]. An advantage of APOE-ε4 at a young age could help explain its persistence in the human population despite slightly negative effects on risk of coronary heart disease [60].

Any behavioral advantages of APOE-ε4 seem to disappear by middle age, with even greater impairment in old age; these effects may be due to the early accumulation of amyloid in APOE-ε4 subjects [2]. APOE-ε4-positive elderly subjects score lower on the NINL and Novel Location tests, suggesting that APOE-ε4 impairs object recognition and spatial memory [48]. In addition, APOE-ε4 carriers show poorer performance in a measure of executive function [51]. APOE may also affect the risk of seizures prior to the development of AD. Seizures are common early in the process of cognitive decline or the development of AD, and the onset of seizures is associated with earlier onset of dementia [61]. Inheritance of APOE-ε4 may lead to earlier onset of chronic seizures [62] and increase the risk of epilepsy after traumatic brain injury [63]. Thus, behavioral performance differences between cognitively normal APOE-ε4 carriers in published studies may be due to the age of subjects; specifically, older APOE-ε4 carriers may have accumulated underlying pathology with age impairing performance compared to non-APOE-ε4 carriers.

3.2.2 Effects of APOE genotype on human brain structure—Consistent with the more extensive data in mouse brains, hippocampal neurons from APOE-ε3/ε4 humans in their eighties without post-mortem evidence of AD pathology have lower dendritic spine density [64]. APOE-ε4 carriers at birth have reduced grey matter volume in temporal areas and increased grey matter volume in frontal areas, suggesting early developmental differences in brain structure dependent on APOE genotype [65; 66]. In young healthy APOE-ε4 carriers (average age of 20–25 years), white and grey matter volumes in the medial temporal lobe (MTL) were reported to be either larger [67], unchanged [56; 68–70] or smaller [71; 72]. There are no differences, however, in the temporal cortex or hippocampus of middle-aged adults, although APOE-ε4 carriers had thinner frontal cortices, while APOE-ε2 carriers had thicker parahippocampal cortices [73; 74]. As the average age of subjects increase from 40 to 65 years of age, MTL volumes in APOE-ε4 carriers decrease compared to non APOE-ε4 carriers [74–76]. In later ages, APOE-ε4 is associated with accelerated brain atrophy in the MTL with AD [77–79]. Overall, these data suggest that the MTL develops differently in APOE-ε4 carriers from birth, and any subtle differences in the MTL disappear as more dramatic APOE effects on AD pathology and MTL volume develop later in life.

3.2.3 Effects of APOE genotype on human brain function—Like behavior, brain function in APOE-ε4 carriers may also be altered prior to AD symptom onset. FDG-PET studies in healthy individuals show reduced glucose utilization in APOE-ε4 positive individuals [80–82]. In college-aged APOE-ε4 carriers, $H_2{}^{15}O$ PET uptake is decreased in the left right superior temporal and left fusiform gyri, but increased in the left middle temporal and right transverse temporal gyri during a non-verbal memory task [83]. As aging progresses, these increases disappear. Subjects 50–63 years of age with a family history of AD have a decline in glucose metabolism in the temporal cortex and parahippocampal gyrus when imaged before and after a 2 year interval [81]. During a non-verbal memory task, cognitively intact elderly APOE-ε4 carriers have altered temporal lobe activation as measured by $H_2{}^{15}O$ PET [82]. In a study of cognitively normal subjects of 30–95 years of age, APOE-ε4 carriers have a lower uptake of FDG-PET several brain regions, including the temporal lobe [80]. However, APOE-ε4 carriers who were highly active and exercised

regularly have greater temporal lobe activation when compared to sedentary carriers [84], implying that behavior and lifestyle influence effects of APOE genotype. Overall, brain activation may be increased in select brain areas in young APOE-ε4 carriers, but decreased in healthy older APOE-ε4 carriers, perhaps due to underlying age-related pathology.

Functional MRI (fMRI) studies found an increased level of brain activity in the default mode network in APOE-ε4 individuals at 20–35 years old in the MTL [85]. This study also found that there is more activation in the hippocampus in APOE-ε4 carriers during an encoding task [85]; other studies showed differences in MTL activation by APOE genotype during diverse behavioral tasks [57; 86; 87]. In cognitively normal healthy young adults, APOE4 carriers had reduced grid-cell-like representations in the entorhinal cortex, an area of the MTL affected early in AD, but increased hippocampal activation [88]. Similar to the findings with PET imaging, it appears that brain activation may be increased in select brain areas in APOE4 carriers, perhaps as a compensatory response for low activation other brain areas [88]. It is hypothesized that MTL activation may be increased in younger APOE-ε4 carriers but decreased in older APOE-ε4 carriers [89], and that this activity is dependent on task difficulty: healthy middle-aged APOE-ε4 carriers have more instances of higher activation compared to non-carriers in a low demand working memory task, but not in moderate to high demand tasks [90].

These studies support a model of APOE-ε4 in young adults being associated with higher MTL activity and equal or improved cognition, but that with aging (and development of AD pathological changes), MTL activity and cognitive performance decreases. This model could be tested in analysis of APOE4 mouse models over time, or it could be addressed in humans with more in depth analysis of MTL-related behaviors and brain activity at different ages. The phenotypes associated with APOE-ε4 also could be studied in future work on young adults to investigate whether socioeconomic and environmental effects interact with APOE-ε4 to alter cognition and brain function. In addition, studies with more participants using uniform methods and exclusion criteria would also further clarify conflicting results from existing studies. Together, these studies suggest that APOE4 may predispose the brain to AD pathology later in life by increasing MTL activity over decades. Further investigation of differences in brain activity associated with APOE genotype may aid in identifying new biomarkers of AD risk, allowing development of preventative approaches aimed at modifying these biomarkers.

4. MECHANISMS OF EFFECTS OF APOE GENOTYPE EFFECTS

The consistent findings in studies of mouse models and young humans have lead to the development of several hypotheses of how APOE genotype may affect normal brain function. Four considered here are that APOE genotype affects levels of apoE, lipidation of apoE, brain inflammation, and neuronal hyperexcitability.

4.1 Levels of apoE isoforms

In mice, the apoE4 protein is reproducibly found at lower levels in the brain and blood compared to apoE3 or apoE2 [41; 91; 92], although levels of APOE mRNA are unaffected [92]. Lower apoE4 levels may be due to impaired folding and increased degradation of

apoE4 in astrocytes compared to apoE2 and apoE3 [93]. In humans, APOE-ε4 is associated with lower apoE levels and APOE-ε2 with higher apoE levels both in CSF [94], and in plasma [94; 95]. Levels of CSF and plasma apoE did not correlate well with each other, but CSF apoE levels are correlated to CSF $A\beta_{42}$ levels [94]. In a large prospective study, low plasma apoE levels correlate with increased risk of AD, controlling for APOE genotype [96]. These studies suggest that APOE-ε4 may contribute to increased AD risk by reducing total apoE levels. Decreased apoE would diminish the normal apoE functions, and could be responsible for reductions in synaptic density and the associated behavioral deficits [19]

4.2 ApoE lipidation

The overall level of apoE may not be as important is its form in lipoproteins. Brain apoE is secreted by astrocytes [97] as part of discoidal lipoproteins [98], which mature into high density lipoproteins in the CSF [99]. Secreted apoE is lipidated through interactions with the ABCA1 transporter [100]. Studies of viral expression of APOE show that brain apoE4 is lipidated significantly less than apoE2 [101]. Activation of apoE production and lipidation can occur through the LXR/RXR system, which induces expression of both APOE and ABCA1 [102]. Treatment of AD mouse models with LXR agonists reduces Aβ levels and improves cognition [103–105]. Treatment with the RXR agonist bexarotene also improves Aβ clearance and cognition [106], in a manner dependent on the presence of both APOE [106] and ABCA1 [107]. Other treatments to improve apoE4 lipidation (e.g., microRNA-33 induction [108], retinoic acid [109]) could prove useful in preventing brain phenotypes associated with APOE4 and neurodegeneration.

4.3 Neuroinflammation

Functional apoE could also protect the brain from inflammatory processes. ApoE reduces the inflammatory responses of macrophages [110; 111] and microglia [112] in vitro, and APOE4 TR mice are susceptible to brain damage related to inflammatory processes such as experimental autoinflammatory encephalitis [113], traumatic brain injury [114], and lipopolysaccharide (LPS) exposure [111; 115]. After LPS exposure, the APOE4 genotype in mice is associated with higher levels of pro-inflammatory cytokines [116], enhanced NF-kB signaling [117] and increased loss of synaptic markers [115]. Chronic low-level brain inflammation in the presence of apoE4 could leave the brain more susceptible to injuries that accumulate with aging [111; 118]. This hypothesis would suggest that anti-inflammatory approaches may be more effective in protecting humans with APOE-ε4 from brain damages. Indeed, the protective effects of non-steroidal anti-inflammatory drugs (NSAIDs) against risk of AD are limited to individuals with APOE-ε4 [119].

4.4 Hyperexcitability

The alterations of pre- and post-synaptic molecules associated with APOE genotype could lead to aberrant hippocampal function. APOE4 TR mice have higher levels of excitatory synaptic activity in amygdala neurons compared to other APOE genotypes [38]. APOE4 TR mice show an increased risk of seizures and synchronous hippocampal neurons firing, as well as a greater sensitivity to treatment with a drug to induce seizures [120]. Treatment with an RXR agonist reduced epileptiform spiking seen in mouse models of AD and epilepsy unrelated to APOE genotype [121]. Aged female APOE4 mice have fewer interneurons in

the hippocampal hilus [37], also altering the excitability of the dentate gyrus. Hyperexcitability associated with APOE-ε4 could lead to hippocampal damage, predisposing to AD and thus, anti-seizure approaches could prove useful in preventing AD associated with inheritance of APOE-ε4.

5. CONCLUSION

APOE genotype is recognized as the strongest genetic risk factor of AD [122; 123]. The recent studies outlined here support the hypothesis that APOE genotype is also associated with differences in normal brain function early in life before brain amyloid accumulates. Animal studies have demonstrated that while APOE4 TR mice lack classical AD pathological changes, they have impairments in behaviors dependent on the hippocampus, and show gross changes to neuronal morphology and brain biochemistry. Human studies have shown that the brain develops differently in APOE-ε4 carriers from birth, such that brain activation may be increased in select brain areas in young APOE-ε4 carriers. As APOE-ε4 carriers reach ages of amyloid accumulation, decreases in glucose utilization, brain activity and gray matter occur. These brain differences associated with APOE genotype may arise from effects on apoE levels, apoE lipidation, brain inflammation, or hippocampal hyperexcitability prior to the development of AD pathological changes. Whether these early effects of APOE are related to the later development of AD is unknown, but, importantly, several of them have been shown to be altered by diet or drugs. Studies of APOE-ε4 positive individuals early in life could lead to the identification of new biomarkers of AD risk not associated with AD pathological changes, and these biomarkers would allow very early preventative therapies to be tested in APOE-ε4 positive individuals.

References

1. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012; 367(9):795–804. [PubMed: 22784036]
2. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. Jama. 2015; 313(19): 1924–38. [PubMed: 25988462]
3. Sperling R, Mormino E, Johnson K. The evolution of preclinical Alzheimer's disease: implications for prevention trials. Neuron. 2014; 84(3):608–22. [PubMed: 25442939]
4. Quiroz YT, Schultz AP, Chen K, Protas HD, Brickhouse M, Fleisher AS, et al. Brain Imaging and Blood Biomarker Abnormalities in Children With Autosomal Dominant Alzheimer Disease: A Cross-Sectional Study. JAMA neurology. 2015
5. Mahley RW, Rall SC Jr, Apolipoprotein E. far more than a lipid transport protein. Annu Rev Genomics Hum Genet. 2000; 1:507–37. [PubMed: 11701639]
6. Serrano-Pozo A, Qian J, Monsell SE, Betensky RA, Hyman BT. APOEepsilon2 is associated with milder clinical and pathological Alzheimer disease. Ann Neurol. 2015; 77(6):917–29. [PubMed: 25623662]
7. Naj AC, Jun G, Reitz C, Kunkle BW, Perry W, Park YS, et al. Effects of multiple genetic loci on age at onset in late-onset Alzheimer disease: a genome-wide association study. JAMA neurology. 2014; 71(11):1394–404. [PubMed: 25199842]
8. Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, et al. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N Engl J Med. 2009; 361(3):255–63. [PubMed: 19605830]

9. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol. 2013; 12(4):357–67. [PubMed: 23477989]
10. Nelson PT, Pious NM, Jicha GA, Wilcock DM, Fardo DW, Estus S, et al. APOE-epsilon2 and APOE-epsilon4 correlate with increased amyloid accumulation in cerebral vasculature. J Neuropathol Exp Neurol. 2013; 72(7):708–15. [PubMed: 23771217]
11. Rebeck GW, Reiter JS, Strickland DK, Hyman BT. Apolipoprotein E in sporadic Alzheimer's disease: allelic variation and receptor interactions. Neuron. 1993; 11(4):575–80. [PubMed: 8398148]
12. Tai LM, Bilousova T, Jungbauer L, Roeske SK, Youmans KL, Yu C, et al. Levels of soluble apolipoprotein E/amyloid-beta (Abeta) complex are reduced and oligomeric Abeta increased with APOE4 and Alzheimer disease in a transgenic mouse model and human samples. The Journal of biological chemistry. 2013; 288(8):5914–26. [PubMed: 23293020]
13. Lautner R, Palmqvist S, Mattsson N, Andreasson U, Wallin A, Palsson E, et al. Apolipoprotein E genotype and the diagnostic accuracy of cerebrospinal fluid biomarkers for Alzheimer disease. JAMA Psychiatry. 2014; 71(10):1183–91. [PubMed: 25162367]
14. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron. 2009; 63(3):287–303. [PubMed: 19679070]
15. Youmans KL, Tai LM, Nwabuisi-Heath E, Jungbauer L, Kanekiyo T, Gan M, et al. APOE4-specific changes in Abeta accumulation in a new transgenic mouse model of Alzheimer disease. The Journal of biological chemistry. 2012; 287(50):41774–86. [PubMed: 23060451]
16. Manning EN, Barnes J, Cash DM, Bartlett JW, Leung KK, Ourselin S, et al. APOE epsilon4 is associated with disproportionate progressive hippocampal atrophy in AD. PLoS One. 2014; 9(5):e97608. [PubMed: 24878738]
17. Wolk DA, Dickerson BC, Neuroimaging AsD. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107(22):10256–61. [PubMed: 20479234]
18. Huang Y, Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. Neurobiology of disease. 2014; 72(Pt A):3–12. [PubMed: 25173806]
19. Mauch DH, Nagler K, Schumacher S, Goritz C, Muller EC, Otto A, et al. CNS synaptogenesis promoted by glia-derived cholesterol. Science. 2001; 294(5545):1354–7. [PubMed: 11701931]
20. Zhang SH, Reddick RL, Piedrahita JA, Maeda N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science. 1992; 258(5081):468–71. [PubMed: 1411543]
21. Plump AS, Smith JD, Hayek T, Aalto-Setala K, Walsh A, Verstuyft JG, et al. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell. 1992; 71(2):343–53. [PubMed: 1423598]
22. 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; 71(10):1228–36. [PubMed: 25111166]
23. Buttini M, Orth M, Bellosta S, Akeefe H, Pitas RE, Wyss-Coray T, et al. Expression of human apolipoprotein E3 or E4 in the brains of Apoe−/− mice: isoform-specific effects on neurodegeneration. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1999; 19(12):4867–80. [PubMed: 10366621]
24. Hayek T, Oiknine J, Brook JG, Aviram M. Increased plasma and lipoprotein lipid peroxidation in apo E-deficient mice. Biochem Biophys Res Commun. 1994; 201(3):1567–74. [PubMed: 8024602]
25. Raffai RL, Dong LM, Farese RV Jr, Weisgraber KH. Introduction of human apolipoprotein E4 "domain interaction" into mouse apolipoprotein E. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(20):11587–91. [PubMed: 11553788]
26. Sullivan PM, Mezdour H, Aratani Y, Knouff C, Najib J, Reddick RL, et al. Targeted replacement of the mouse apolipoprotein E gene with the common human APOE3 allele enhances diet-induced hypercholesterolemia and atherosclerosis. The Journal of biological chemistry. 1997; 272(29): 17972–80. [PubMed: 9218423]

27. Sullivan PM, Mace BE, Maeda N, Schmechel DE. Marked regional differences of brain human apolipoprotein E expression in targeted replacement mice. Neuroscience. 2004; 124(4):725–33. [PubMed: 15026113]
28. Wang C, Wilson WA, Moore SD, Mace BE, Maeda N, Schmechel DE, et al. Human apoE4-targeted replacement mice display synaptic deficits in the absence of neuropathology. Neurobiology of disease. 2005; 18(2):390–8. [PubMed: 15686968]
29. Liraz O, Boehm-Cagan A, Michaelson DM. ApoE4 induces Abeta42, tau, and neuronal pathology in the hippocampus of young targeted replacement apoE4 mice. Molecular neurodegeneration. 2013; 8:16. [PubMed: 23684315]
30. Rodriguez GA, Burns MP, Weeber EJ, Rebeck GW. Young APOE4 targeted replacement mice exhibit poor spatial learning and memory, with reduced dendritic spine density in the medial entorhinal cortex. Learning & Memory. 2013; 20(5):256–66. [PubMed: 23592036]
31. Salomon-Zimri S, Boehm-Cagan A, Liraz O, Michaelson DM. Hippocampus-related cognitive impairments in young apoE4 targeted replacement mice. Neurodegener Dis. 2014; 13(2–3):86–92. [PubMed: 24080852]
32. Bour A, Grootendorst J, Vogel E, Kelche C, Dodart JC, Bales K, et al. Middle-aged human apoE4 targeted-replacement mice show retention deficits on a wide range of spatial memory tasks. Behav Brain Res. 2008; 193(2):174–82. [PubMed: 18572260]
33. Raber J, Wong D, Buttini M, Orth M, Bellosta S, Pitas RE, et al. Isoform-specific effects of human apolipoprotein E on brain function revealed in ApoE knockout mice: increased susceptibility of females. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95(18):10914–9. [PubMed: 9724804]
34. Raber J, Wong D, Yu GQ, Buttini M, Mahley RW, Pitas RE, et al. Apolipoprotein E and cognitive performance. Nature. 2000; 404(6776):352–4.
35. Siegel JA, Haley GE, Raber J. Apolipoprotein E isoform-dependent effects on anxiety and cognition in female TR mice. Neurobiology of aging. 2012; 33(2):345–58. [PubMed: 20400205]
36. Dumanis SB, Tesoriero JA, Babus LW, Nguyen MT, Trotter JH, Ladu MJ, et al. ApoE4 decreases spine density and dendritic complexity in cortical neurons in vivo. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2009; 29(48):15317–22. [PubMed: 19955384]
37. Andrews-Zwilling Y, Bien-Ly N, Xu Q, Li G, Bernardo A, Yoon SY, et al. Apolipoprotein E4 causes age- and Tau-dependent impairment of GABAergic interneurons, leading to learning and memory deficits in mice. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010; 30(41):13707–17. [PubMed: 20943911]
38. Klein RC, Acheson SK, Mace BE, Sullivan PM, Moore SD. Altered neurotransmission in the lateral amygdala in aged human apoE4 targeted replacement mice. Neurobiology of aging. 2014; 35(9):2046–52. [PubMed: 24698766]
39. Korwek KM, Trotter JH, Ladu MJ, Sullivan PM, Weeber EJ. ApoE isoform-dependent changes in hippocampal synaptic function. Molecular neurodegeneration. 2009; 4:21. [PubMed: 19725929]
40. Trommer BL, Shah C, Yun SH, Gamkrelidze G, Pasternak ES, Ye GL, et al. ApoE isoform affects LTP in human targeted replacement mice. Neuroreport. 2004; 15(17):2655–8. [PubMed: 15570172]
41. Yong SM, Lim ML, Low CM, Wong BS. Reduced neuronal signaling in the ageing apolipoprotein-E4 targeted replacement female mice. Sci Rep. 2014; 4:6580. [PubMed: 25301084]
42. Dumanis SB, DiBattista AM, Miessau M, Moussa CE, Rebeck GW. APOE genotype affects the pre-synaptic compartment of glutamatergic nerve terminals. Journal of neurochemistry. 2013; 124(1):4–14. [PubMed: 22862561]
43. Kariv-Inbal Z, Yacobson S, Berkecz R, Peter M, Janaky T, Lutjohann D, et al. The isoform-specific pathological effects of apoE4 in vivo are prevented by a fish oil (DHA) diet and are modified by cholesterol. J Alzheimers Dis. 2012; 28(3):667–83. [PubMed: 22057027]
44. Barger SW. Apolipoprotein E acts at pre-synaptic sites…among others. Journal of neurochemistry. 2013; 124(1):1–3. [PubMed: 23020739]
45. Ward A, Crean S, Mercaldi CJ, Collins JM, Boyd D, Cook MN, et al. Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. Neuroepidemiology. 2012; 38(1):1–17. [PubMed: 22179327]

46. 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; 278(16): 1349–56. [PubMed: 9343467]
47. Acevedo SF, Piper BJ, Craytor MJ, Benice TS, Raber J. Apolipoprotein E4 and sex affect neurobehavioral performance in primary school children. Pediatr Res. 2010; 67(3):293–9. [PubMed: 19952867]
48. Berteau-Pavy F, Park B, Raber J. Effects of sex and APOE epsilon4 on object recognition and spatial navigation in the elderly. Neuroscience. 2007; 147(1):6–17. [PubMed: 17509769]
49. Haley GE, Berteau-Pavy F, Parkv B, Raber J. Effects of epsilon4 on object recognition in the non-demented elderly. Curr Aging Sci. 2010; 3(2):127–37. [PubMed: 20044903]
50. Yasen AL, Raber J, Miller JK, Piper BJ. Sex, but not Apolipoprotein E Polymorphism, Differences in Spatial Performance in Young Adults. Arch Sex Behav. 2015
51. Luck T, Then FS, Luppa M, Schroeter ML, Arelin K, Burkhardt R, et al. Association of the apolipoprotein E genotype with memory performance and executive functioning in cognitively intact elderly. Neuropsychology. 2015; 29(3):382–7. [PubMed: 25365563]
52. Pendleton N, Payton A, van den Boogerd EH, Holland F, Diggle P, Rabbitt PM, et al. Apolipoprotein E genotype does not predict decline in intelligence in healthy older adults. Neurosci Lett. 2002; 324(1):74–6. [PubMed: 11983298]
53. Taylor AE, Guthrie PA, Smith GD, Golding J, Sattar N, Hingorani AD, et al. IQ, educational attainment, memory and plasma lipids: associations with apolipoprotein E genotype in 5995 children. Biol Psychiatry. 2011; 70(2):152–8. [PubMed: 21215387]
54. Yu YW, Lin CH, Chen SP, Hong CJ, Tsai SJ. Intelligence and event-related potentials for young female human volunteer apolipoprotein E epsilon4 and non-epsilon4 carriers. Neurosci Lett. 2000; 294(3):179–81. [PubMed: 11072144]
55. Jochemsen HM, Muller M, van der Graaf Y, Geerlings MI. APOE epsilon4 differentially influences change in memory performance depending on age. The SMART-MR study. Neurobiology of aging. 2012; 33(4):832 e15–22.
56. Mondadori CR, de Quervain DJ, Buchmann A, Mustovic H, Wollmer MA, Schmidt CF, et al. Better memory and neural efficiency in young apolipoprotein E epsilon4 carriers. Cereb Cortex. 2007; 17(8):1934–47. [PubMed: 17077159]
57. Rusted JM, Evans SL, King SL, Dowell N, Tabet N, Tofts PS. APOE e4 polymorphism in young adults is associated with improved attention and indexed by distinct neural signatures. Neuroimage. 2013; 65:364–73. [PubMed: 23063453]
58. Tuminello ER, Han SD. The apolipoprotein e antagonistic pleiotropy hypothesis: review and recommendations. Int J Alzheimers Dis. 2011; 2011:726197. [PubMed: 21423560]
59. Rusted J, Carare RO. Are the effects of APOE 4 on cognitive function in nonclinical populations age- and gender-dependent? Neurodegener Dis Manag. 2015; 5(1):37–48. [PubMed: 25711453]
60. Bennet AM, Di Angelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. Jama. 2007; 298(11):1300–11. [PubMed: 17878422]
61. Vossel KA, Beagle AJ, Rabinovici GD, Shu H, Lee SE, Naasan G, et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. JAMA neurology. 2013; 70(9):1158–66. [PubMed: 23835471]
62. Briellmann RS, Torn-Broers Y, Busuttil BE, Major BJ, Kalnins RM, Olsen M, et al. APOE epsilon4 genotype is associated with an earlier onset of chronic temporal lobe epilepsy. Neurology. 2000; 55(3):435–7. [PubMed: 10932283]
63. Diaz-Arrastia R, Gong Y, Fair S, Scott KD, Garcia MC, Carlile MC, et al. Increased risk of late posttraumatic seizures associated with inheritance of APOE epsilon4 allele. Arch Neurol. 2003; 60(6):818–22. [PubMed: 12810485]
64. Ji Y, Gong Y, Gan W, Beach T, Holtzman DM, Wisniewski T. Apolipoprotein E isoform-specific regulation of dendritic spine morphology in apolipoprotein E transgenic mice and Alzheimer's disease patients. Neuroscience. 2003; 122(2):305–15. [PubMed: 14614898]

65. Dean DC 3rd, Jerskey BA, Chen K, Protas H, Thiyyagura P, Roontiva A, et al. Brain differences in infants at differential genetic risk for late-onset Alzheimer disease: a cross-sectional imaging study. JAMA neurology. 2014; 71(1):11–22. [PubMed: 24276092]

66. Knickmeyer RC, Wang J, Zhu H, Geng X, Woolson S, Hamer RM, et al. Common variants in psychiatric risk genes predict brain structure at birth. Cereb Cortex. 2014; 24(5):1230–46. [PubMed: 23283688]

67. DiBattista AM, Stevens BW, Rebeck GW, Green AE. Two Alzheimer's disease risk genes increase entorhinal cortex volume in young adults. Front Hum Neurosci. 2014; 8:779. [PubMed: 25339884]

68. Dennis NA, Browndyke JN, Stokes J, Need A, Burke JR, Welsh-Bohmer KA, et al. Temporal lobe functional activity and connectivity in young adult APOE varepsilon4 carriers. Alzheimers Dement. 2010; 6(4):303–11. [PubMed: 19744893]

69. Filippini N, Rao A, Wetten S, Gibson RA, Borrie M, Guzman D, et al. Anatomically-distinct genetic associations of APOE epsilon4 allele load with regional cortical atrophy in Alzheimer's disease. Neuroimage. 2009; 44(3):724–8. [PubMed: 19013250]

70. Matura S, Prvulovic D, Jurcoane A, Hartmann D, Miller J, Scheibe M, et al. Differential effects of the ApoE4 genotype on brain structure and function. Neuroimage. 2014; 89:81–91. [PubMed: 24296331]

71. O'Dwyer L, Lamberton F, Matura S, Tanner C, Scheibe M, Miller J, et al. Reduced hippocampal volume in healthy young ApoE4 carriers: an MRI study. PLoS One. 2012; 7(11):e48895. [PubMed: 23152815]

72. Alexopoulos P, Richter-Schmidinger T, Horn M, Maus S, Reichel M, Sidiropoulos C, et al. Hippocampal volume differences between healthy young apolipoprotein E epsilon2 and epsilon4 carriers. J Alzheimers Dis. 2011; 26(2):207–10. [PubMed: 21606569]

73. Fennema-Notestine C, Panizzon MS, Thompson WR, Chen CH, Eyler LT, Fischl B, et al. Presence of ApoE epsilon4 allele associated with thinner frontal cortex in middle age. J Alzheimers Dis. 2011; 26(Suppl 3):49–60. [PubMed: 21971450]

74. Espeseth T, Westlye LT, Fjell AM, Walhovd KB, Rootwelt H, Reinvang I. Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E epsilon 4. Neurobiology of aging. 2008; 29(3):329–40. [PubMed: 17161508]

75. Alexander GE, Bergfield KL, Chen K, Reiman EM, Hanson KD, Lin L, et al. Gray matter network associated with risk for Alzheimer's disease in young to middle-aged adults. Neurobiology of aging. 2012; 33(12):2723–32. [PubMed: 22405043]

76. Wishart HA, Saykin AJ, McAllister TW, Rabin LA, McDonald BC, Flashman LA, et al. Regional brain atrophy in cognitively intact adults with a single APOE epsilon4 allele. Neurology. 2006; 67(7):1221–4. [PubMed: 17030756]

77. Fei M, Jianhua W. Apolipoprotein epsilon4-allele as a significant risk factor for conversion from mild cognitive impairment to Alzheimer's disease: a meta-analysis of prospective studies. J Mol Neurosci. 2013; 50(2):257–63. [PubMed: 23242623]

78. Shen L, Kim S, Risacher SL, Nho K, Swaminathan S, West JD, et al. Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in MCI and AD: A study of the ADNI cohort. Neuroimage. 2010; 53(3):1051–63. [PubMed: 20100581]

79. Thomann PA, Roth AS, Dos Santos V, Toro P, Essig M, Schroder J. Apolipoprotein E polymorphism and brain morphology in mild cognitive impairment. Dement Geriatr Cogn Disord. 2008; 26(4):300–5. [PubMed: 18843182]

80. Knopman DS, Jack CR Jr, Wiste HJ, Lundt ES, Weigand SD, Vemuri P, et al. 18F-fluorodeoxyglucose positron emission tomography, aging, and apolipoprotein E genotype in cognitively normal persons. Neurobiology of aging. 2014; 35(9):2096–106. [PubMed: 24702820]

81. Reiman EM, Caselli RJ, Chen K, Alexander GE, Bandy D, Frost J. Declining brain activity in cognitively normal apolipoprotein E epsilon 4 heterozygotes: A foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(6):3334–9. [PubMed: 11248079]

82. Scarmeas N, Habeck C, Anderson KE, Hilton J, Devanand DP, Pelton GH, et al. Altered PET functional brain responses in cognitively intact elderly persons at risk for Alzheimer disease

(carriers of the epsilon4 allele). Am J Geriatr Psychiatry. 2004; 12(6):596–605. [PubMed: 15545327]

83. Scarmeas N, Habeck CG, Hilton J, Anderson KE, Flynn J, Park A, et al. APOE related alterations in cerebral activation even at college age. Journal of neurology, neurosurgery, and psychiatry. 2005; 76(10):1440–4.
84. Deeny SP, Poeppel D, Zimmerman JB, Roth SM, Brandauer J, Witkowski S, et al. Exercise, APOE, and working memory: MEG and behavioral evidence for benefit of exercise in epsilon4 carriers. Biol Psychol. 2008; 78(2):179–87. [PubMed: 18395955]
85. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, et al. Distinct patterns of brain activity in young carriers of the APOE-epsilon 4 allele. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(17):7209–14. [PubMed: 19357304]
86. Borghesani PR, Johnson LC, Shelton AL, Peskind ER, Aylward EH, Schellenberg GD, et al. Altered medial temporal lobe responses during visuospatial encoding in healthy APOE*4 carriers. Neurobiology of aging. 2008; 29(7):981–91. [PubMed: 17350142]
87. Green AE, Gray JR, Deyoung CG, Mhyre TR, Padilla R, Dibattista AM, et al. A combined effect of two Alzheimer's risk genes on medial temporal activity during executive attention in young adults. Neuropsychologia. 2014; 56:1–8. [PubMed: 24388797]
88. Kunz L, Schroder TN, Lee H, Montag C, Lachmann B, Sariyska R, et al. Reduced grid-cell-like representations in adults at genetic risk for Alzheimer's disease. Science. 2015; 350(6259):430–3. [PubMed: 26494756]
89. Filippini N, Ebmeier KP, MacIntosh BJ, Trachtenberg AJ, Frisoni GB, Wilcock GK, et al. Differential effects of the APOE genotype on brain function across the lifespan. Neuroimage. 2011; 54(1):602–10. [PubMed: 20705142]
90. Chen CJ, Chen CC, Wu D, Chi NF, Chen PC, Liao YP, et al. Effects of the apolipoprotein E epsilon4 allele on functional MRI during n-back working memory tasks in healthy middle-aged adults. AJNR Am J Neuroradiol. 2013; 34(6):1197–202. [PubMed: 23275593]
91. Riddell DR, Zhou H, Atchison K, Warwick HK, Atkinson PJ, Jefferson J, et al. Impact of apolipoprotein E (ApoE) polymorphism on brain ApoE levels. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2008; 28(45):11445–53. [PubMed: 18987181]
92. Sullivan PM, Han B, Liu F, Mace BE, Ervin JF, Wu S, et al. Reduced levels of human apoE4 protein in an animal model of cognitive impairment. Neurobiology of aging. 2011; 32(5):791–801. [PubMed: 19577821]
93. Zhong N, Weisgraber KH. Understanding the basis for the association of apoE4 with Alzheimer's disease: opening the door for therapeutic approaches. Curr Alzheimer Res. 2009; 6(5):415–8. [PubMed: 19874264]
94. Cruchaga C, Kauwe JS, Nowotny P, Bales K, Pickering EH, Mayo K, et al. Cerebrospinal fluid APOE levels: an endophenotype for genetic studies for Alzheimer's disease. Hum Mol Genet. 2012; 21(20):4558–71. [PubMed: 22821396]
95. Martinez-Morillo E, Hansson O, Atagi Y, Bu G, Minthon L, Diamandis EP, et al. Total apolipoprotein E levels and specific isoform composition in cerebrospinal fluid and plasma from Alzheimer's disease patients and controls. Acta Neuropathol. 2014; 127(5):633–43. [PubMed: 24633805]
96. Rasmussen KL, Tybjaerg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. Plasma levels of apolipoprotein E and risk of dementia in the general population. Ann Neurol. 2015; 77(2):301–11. [PubMed: 25469919]
97. Boyles JK, Pitas RE, Wilson E, Mahley RW, Taylor JM. Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system. The Journal of clinical investigation. 1985; 76(4):1501–13. [PubMed: 3932467]
98. 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; 70(5):2070–81. [PubMed: 9572293]
99. 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; 262(29):14352–60. [PubMed: 3115992]

100. Lee J, Bu G. Genetics and molecular biology: ABCA1 in brain apolipoprotein E metabolism and lipidation. Current opinion in lipidology. 2005; 16(1):115–7. [PubMed: 15650570]
101. Hu J, Liu CC, Chen XF, Zhang YW, Xu H, Bu G. Opposing effects of viral mediated brain expression of apolipoprotein E2 (apoE2) and apoE4 on apoE lipidation and Abeta metabolism in apoE4-targeted replacement mice. Molecular neurodegeneration. 2015; 10:6. [PubMed: 25871773]
102. Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ, et al. LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(2): 507–12. [PubMed: 11149950]
103. 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; 280(6):4079–88. [PubMed: 15557325]
104. Riddell DR, Zhou H, Comery TA, Kouranova E, Lo CF, Warwick HK, et al. The LXR agonist TO901317 selectively lowers hippocampal Abeta42 and improves memory in the Tg2576 mouse model of Alzheimer's disease. Molecular and cellular neurosciences. 2007; 34(4):621–8. [PubMed: 17336088]
105. 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; 285(44):34144–54. [PubMed: 20739291]
106. 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; 335(6075):1503–6. [PubMed: 22323736]
107. Corona AW, Kodoma N, Casali BT, Landreth GE. ABCA1 is Necessary for Bexarotene-Mediated Clearance of Soluble Amyloid Beta from the Hippocampus of APP/PS1 Mice. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2015
108. Kim J, Yoon H, Horie T, Burchett JM, Restivo JL, Rotllan N, et al. microRNA-33 Regulates ApoE Lipidation and Amyloid-beta Metabolism in the Brain. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2015; 35(44):14717–26. [PubMed: 26538644]
109. Zhao J, Fu Y, Liu CC, Shinohara M, Nielsen HM, Dong Q, et al. Retinoic acid isomers facilitate apolipoprotein E production and lipidation in astrocytes through the retinoid X receptor/retinoic acid receptor pathway. The Journal of biological chemistry. 2014; 289(16):11282–92. [PubMed: 24599963]
110. Li K, Ching D, Luk FS, Raffai RL. Apolipoprotein E Enhances MicroRNA-146a in Monocytes and Macrophages to Suppress Nuclear Factor-kappaB-Driven Inflammation and Atherosclerosis. Circ Res. 2015; 117(1):e1–e11. [PubMed: 25904598]
111. Vitek MP, Brown CM, Colton CA. APOE genotype-specific differences in the innate immune response. Neurobiology of aging. 2009; 30(9):1350–60. [PubMed: 18155324]
112. Pocivavsek A, Burns MP, Rebeck GW. Low-density lipoprotein receptors regulate microglial inflammation through c-Jun N-terminal kinase. Glia. 2009; 57(4):444–53. [PubMed: 18803301]
113. Tu JL, Zhao CB, Vollmer T, Coons S, Lin HJ, Marsh S, et al. APOE 4 polymorphism results in early cognitive deficits in an EAE model. Biochem Biophys Res Commun. 2009; 384(4):466–70. [PubMed: 19422789]
114. Friedman G, Froom P, Sazbon L, Grinblatt I, Shochina M, Tsenter J, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology. 1999; 52(2):244–8. [PubMed: 9932938]
115. 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; 60(4):559–69. [PubMed: 22228589]

116. 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; 278(49):48529–33. [PubMed: 14507923]

117. Ophir G, Amariglio N, Jacob-Hirsch J, Elkon R, Rechavi G, Michaelson DM. Apolipoprotein E4 enhances brain inflammation by modulation of the NF-kappaB signaling cascade. Neurobiology of disease. 2005; 20(3):709–18. [PubMed: 15979312]

118. Colton CA, Needham LK, Brown C, Cook D, Rasheed K, Burke JR, et al. APOE genotype-specific differences in human and mouse macrophage nitric oxide production. J Neuroimmunol. 2004; 147(1–2):62–7. [PubMed: 14741429]

119. 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; 70(1):17–24. [PubMed: 18003940]

120. Hunter JM, Cirrito JR, Restivo JL, Kinley RD, Sullivan PM, Holtzman DM, et al. Emergence of a seizure phenotype in aged apolipoprotein epsilon 4 targeted replacement mice. Brain Res. 2012; 1467:120–32. [PubMed: 22682924]

121. Bomben V, Holth J, Reed J, Cramer P, Landreth G, Noebels J. Bexarotene reduces network excitability in models of Alzheimer's disease and epilepsy. Neurobiology of aging. 2014; 35(9): 2091–5. [PubMed: 24767949]

122. 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; 90(5):1977–81. [PubMed: 8446617]

123. Genin E, Hannequin D, Wallon D, Sleegers K, Hiltunen M, Combarros O, et al. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. Molecular psychiatry. 2011; 16(9):903–7. [PubMed: 21556001]