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Roles of Apolipoprotein E in Alzheimer's Disease and Other Neurological Disorders

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Summary

Apolipoprotein E (ApoE) is a 299 amino acid protein encoded by the *APOE* gene. Three common polymorphisms in the *APOE* gene, ε2, ε3, and ε4, result in single amino changes in the ApoE protein. The *APOE*ε2, ε3, and ε4 alleles strongly and dose-dependently alter the likelihood of developing Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA). In particular, *APOE* ε4 is associated with increased risk for AD, whereas *APOE*ε2 is associated with decreased risk. The effects of *APOE* genotype on AD and CAA risk are likely mediated, in large part, by differential effects of the ApoE protein on amyloid-β (Aβ) accumulation in the brain and cerebrovasculature. Recent data indicate that responses to AD treatments may differ according to *APOE* genotype. The *APOE* ε4 allele is also associated with poor outcome following traumatic brain injury and brain hemorrhage, though the mechanisms underlying these associations are unclear. Given the convincing body of literature tying *APOE* genotype to AD and CAA risk, *APOE* has also been studied in relation to other neurological diseases. While the possibility that *APOE* plays a role in these diseases is of great interest, convincing associations have not yet emerged.

Introduction

With few efficacious treatment options available, the management of many neurological disorders presents clinicians with significant challenges, while healthcare systems are burdened with enormous strain. Understanding environmental and/or genetic components that modulate neurological disease risk and outcome may provide useful information for managing these devastating diseases. Following a series of landmark studies identifying the strong association of the *APOE* ε4 allele with increased AD risk and decreased age of onset and the protective role of the *APOE* ε2 allele,[1–5] numerous studies have investigated

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Search Strategy and Selection Criteria: PubMed was accessed to identify original and review articles published up to December 2010, with the terms "ApoE AND neurological disorders," "ApoE AND Alzheimer's disease," "ApoE AND drug AND AD," "ApoE AND cerebral amyloid angiopathy," "ApoE AND traumatic brain injury," "ApoE AND stroke," "ApoE AND and Down's syndrome," "ApoE AND vascular dementia," "ApoE AND Lewy body dementia," "ApoE AND inclusion-body myositis," "ApoE AND Creutzfeldt-Jakob disease," "ApoE AND multiple sclerosis," "ApoE and amyotrophic lateral sclerosis," "ApoE AND Parkinson's disease," "ApoE AND cerebral palsy," "ApoE AND Huntington's disease," "ApoE AND epilepsy," "ApoE AND Frontotemporal dementia," "ApoE AND Dementia." Only papers published in English were reviewed.

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putative associations of *APOE* genotype with risk or progression for a wide variety of neurological disorders. Given the various proposed roles of apoE in influencing Aβ metabolism, CNS lipid homeostasis, synaptic activity, response to cellular injury, and neuroinflammation, these investigations were hypothesized to reveal strong associations with several diseases. To date, however, AD and CAA are the only neurological diseases for which the level of evidence for an association between *APOE* genotype and disease risk and age of onset is compelling. *APOE* is believed to be linked to AD and CAA risk through isoform-dependent modulation of Aβ accumulation. Associations of *APOE* with outcome following traumatic brain injury (TBI) and risk of Down's syndrome-associated dementia (DAD) are also hypothesized to be, in part, mediated through isoform-dependent modulation of Aβ accumulation. To date, roles for *APOE* genotype in stroke, vascular dementia (VaD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and others have been suggested, but strong consensus has been lacking. This Review evaluates the level of evidence for associations of *APOE* genotype with risk and outcome for various neurological diseases with particular attention to AD and CAA, for which evidence of an association is strong (Table 1). The many proposed roles of apoE in the nervous system present a unique challenge to understanding its roles in neurological disease pathogenesis as well as in treatment strategies. Differences in treatment response according to *APOE* status in recent AD clinical trials will also be evaluated.

Physiological function of apoE

Human apolipoprotein E (apoE) is a lipoprotein of 299 amino acids expressed in multiple organs with the highest expression in liver followed by the brain.[6] ApoE exists mainly as a component of lipoprotein complexes along with other apolipoproteins and proteins in plasma and cerebrospinal fluid (CSF).[6] In humans, there are three polymorphic forms of apoE: apoE2 (Cys-112, Cys-158), apoE3 (Cys-112, Arg-158), and apoE4 (Arg-112, Arg-158).[7] The amino acid differences at these positions are suggested to be critical as they alter the charge and structural properties of the protein, ultimately influencing the functional properties of apoE isoforms.[6]

ApoE is one of the key lipoproteins of lipoprotein complexes that regulate the metabolism of lipids by directing their transport, delivery, and distribution from one tissue or cell type to another through apoE receptors and proteins associated with lipid transfer and lipolysis.[6, 8] The apoE isoform-specific associations with lipoprotein complexes in the plasma and uptake of apoE lipoprotein complexes by LDL receptors have significant effects on peripheral lipid metabolism, having important implications in diseases like Type III Hyperlipoproteinemia (HLP) and atherosclerosis. In brain, apoE is mostly produced by astrocytes, followed by microglial cells and, under certain conditions, by neurons.[9] In the CSF, apoE is associated predominantly with cholesterol and phospholipid-rich, high-density lipoprotein (HDL)-like complexes. Unlike plasma, CSF exclusively contains HDL-like lipoproteins and no LDL or VLDL. ApoE's association with HDL-like particles in the CSF occurs without any known isoform specificity.[10–12] Unlike in the periphery, where apoE isoforms differentially alter lipoprotein metabolism, there is no convincing evidence that apoE isoforms differentially influence general measures of CNS cholesterol or phospholipid metabolism, suggesting that structural differences in apoE isoforms may influence neurological disorders via mechanisms not directly linked to isoform-specific effects on lipid metabolism.

APOE and Alzheimer's disease (AD)

AD is a devastating neurodegenerative disease affecting approximately 26 million people worldwide. AD is pathologically defined by the extracellular accumulation of Aβ, intracellular accumulation of tau, neuronal and synaptic loss, brain atrophy, and

inflammation.[13] Mutations in three genes, *APP*, *PS1*, and *PS2* cause rare forms of autosomal-dominant familial AD with clinical onset typically between the ages of 30–60.[13] Several susceptibility genes have also been implicated in influencing AD risk, one of which, *APOE*, has been confirmed to confer risk for sporadic, late-onset AD (age > 60), as well as autosomal-dominant familial AD.[1, 14] The *APOE* ε3 allele is the most frequent in all populations, with a frequency range of 50–90%, whereas *APOE* ε4 and *APOE* ε2 allele frequencies range from 5–35% and 1–5%, respectively.[6] Risk for AD is associated with *APOE* allele (*ε4 >ε3>ε2*), with the *APOE* ε4 allele present in ~50% of patients who develop late-onset AD compared to 20–25% in controls.[1–3] Having one or two copies of the *APOE* ε4 allele increases late-onset AD risk approximately 3- or 12-fold, respectively. Moreover, having one or two copies of *APOE* ε4 shifts the age of onset earlier by approximately one to two decades relative to non-carriers in late-onset AD.[1] *APOE* ε4 also results in earlier onset of dementia in individuals with a *PS1* mutation in a large Colombian kindred [14]. *APOE* ε2 individuals have reduced risk for developing late-onset AD.[1–3, 14–15] Multiple epidemiological studies from various populations have confirmed the increased frequency of the *APOE* ε4 allele in late-onset AD patients compared to non-carriers, though the frequency varies in different ethnicities.[4] It is important to note that *APOE* ε4 is neither necessary nor sufficient for the development of AD so that apoE polymorphism cannot be utilized alone for the diagnosis of AD.[16–17]

There is controversy as to whether *APOE* polymorphism associates with the rate of progression of cognitive decline in AD after its onset.[3, 18] In particular, there is discrepancy as to the role of *APOE* ε4 in the rate of cognitive and functional decline after dementia onset in AD. Several reports suggest that homozygous *APOE* ε4 patients experience more rapid cognitive and functional decline following clinical disease onset,[3] suggesting that the factors determining disease onset may also have a role in the rate of progression and clinical outcome. Others have also reported that disease onset and rate of progression as factors are different in the context of *APOE* ε4.[3, 19–20] An MRI study from a large, cognitively normal population suggested that *APOE* ε4-carriers have decreased entorhinal cortex volume in children and adolescents, suggesting a potential developmental effect.[21] Longitudinal MRI studies of subjects already diagnosed with AD revealed that the rate of volume decrease of entorhinal cortex and hippocampus is greater in those who are *APOE* ε4-positive.[22] Conversely, a recent study reported that cognitively normal *APOE* ε2-carriers had slower hippocampal atrophy measured over two years compared to non-carriers.[23] A recent large study of cognitively normal individuals found that age-related memory decline starting in the late fifties was greater in *APOE* ε4-carriers vs. non-carriers,[24] suggesting that the consequences of AD pathology may manifest in the brain as early as the sixth decade of life. The role of *APOE* in the predisposition of AD is well established, though further studies are needed to understand the possible association of *APOE* with rate of AD progression.

APOE and cerebral amyloid angiopathy (CAA)

CAA co-occurs in patients with late-onset AD, though a substantial number of individuals develop symptomatic CAA in the absence of dementia. CAA is pathologically characterized by the accumulation of Aβ, mostly Aβ40, in the adventitia and media of penetrating arterioles and in arterioles of the leptomeninges in the CNS.[25–26] CAA is a frequent cause of lobar hemorrhage in individuals over the age of 60. The fact that Aβ deposits are present in brain parenchyma in AD and in vessels in CAA has motivated several investigations to understand the role of apoE isoforms in CAA. *APOE* ε4 is associated with sporadic CAA risk and risk for brain hemorrhage, the severity of which is *APOE* ε4 dose-dependent.[25, 27–31] Interestingly, while *APOE* ε4 is associated with an increase in ICH, the *APOE* ε2 allele appears to predispose individuals to ICH if CAA is present,[32] possibly due to the CAA-related vasculopathic abnormalities associated with this allele.[25] Though the

association of *APOE* ε4 with CAA is well established in several studies, [25, 27–31] there are a few conflicting reports.[32–34] Possible reasons for discrepancies include diversity in genetic background of the populations studied, difference in the proportion of AD and non-AD cases with CAA, and the high mortality rate associated with *APOE* ε4 after CAA-related ICH in post-mortem studies.

Aβ-dependent roles for apoE in AD and CAA

A variety of in vitro and animal studies have demonstrated that apoE plays an important role in determining whether and when Aβ converts from a monomeric, non-toxic molecule into higher molecular weight forms, such as oligomers and fibrils, of which certain forms likely mediate toxicity.[35–37] For example, in mice engineered to develop Aβ plaque and CAA pathology, apoE is required for the formation of these pathologies in addition to Aβ-associated toxicity, e.g., dystrophic neurite formation and CAA-associated hemorrhages.[38–40] Furthermore, expressing human apoE in these models results in apoE isoform-dependent differences in Aβ accumulation (E4>E3>E2).[41–44] Whether Aβ toxicity in the brain is due to small Aβ oligomers or larger aggregates such as fibrils, or both, is unclear, though there is evidence that apoE isoforms can influence both Aβ fibril formation and the toxicity of Aβ oligomers.[45] Though it is likely that CAA and AD share common mechanistic pathways with regard to apoE and Aβ, specific mechanisms have also been suggested in animal studies. For example, in mice, *APOE ε*4 was found to promote the development of CAA probably via increasing the ratio of Aβ40 to Aβ42 in the brain, which results in a shift of Aβ accumulation from the brain parenchyma to vessels[43]. Further, it has been suggested that apoE may influence Aβ drainage through perivascular channels.[46]

In vitro, animal, and human studies suggest that the accumulation of Aβ in the brain is a driving force for AD pathogenesis.[13] While the mechanism by which apoE isoforms affect AD risk is not entirely understood, there is strong evidence that apoE isoforms differentially modulate Aβ metabolism and accumulation. In postmortem tissue from AD patients, apoE is present in Aβ plaques, a major hallmark of AD pathology.[47] Several studies have observed an increase in senile and neuritic plaques in *APOE ε*4 homozygous AD patients compared to *APOE ε*4/*ε*3 or *APOE ε*3 homozygous AD patients and increased plaques in *APOE* ε4-positive vs. ε4-negative patients.[48–52] However, one group found no significant effect on plaque density or number.[9] In a large cohort study in autopsy-confirmed AD patients, the presence of both *APOE ε*4 alleles was found to be a crucial factor in increasing neuritic plaque accumulation in all neocortical areas of brain. *APOE ε2* AD patients had reduced plaque accumulation, though the sample size was very small.[17] Perhaps most relevant in understanding how *APOE* genotype influences AD risk is whether it influences AD pathology in relation to the time course of disease onset. Converging evidence suggests that the initial pathological feature of AD is Aβ deposition in the brain, which is estimated to begin 10–15 years prior to the onset of any clinical signs and symptoms of cognitive decline.[53] Various events appear downstream of Aβ deposition in the AD pathological process, including neurofibrillary tangle formation, neuroinflammation, and neuronal/synaptic loss. The period of AD pathological changes in the absence of clinically detectable disease has been termed “preclinical” or “presymptomatic” AD. If *APOE* genotype is linked to AD risk by influencing the probability of onset of Aβ accumulation, it would be expected that cognitively normal individuals at a given age would have greater brain Aβ burden in the order, *ε4 >ε3>ε2*. In fact, in both CSF biomarker and amyloid imaging studies, isoform-dependent brain Aβ pathology (*ε4 >ε3>ε2)* has been reported in cognitively normal individuals aged 45–90.[23, 54–56] These data suggest that *APOE* genotype modulates AD risk by affecting the likelihood that Aβ begins to deposit, such that the timing of Aβ accumulation is shifted earlier or later in the preclinical phase depending on *APOE* genotype (Figure 1). Given the clear effect of *APOE* in modulating AD risk and Aβ pathology, a

major hypothesis for which there is accumulating evidence is that apoE4 increases Aβ aggregation and/or impairs Aβ clearance relative to other apoE isoforms.

Aβ-independent roles for apoE in AD

While the differential effects of apoE isoforms on lipid metabolism are well-characterized in the periphery, it remains unclear whether apoE isoforms have isoform-specific effects via lipoprotein receptors and transporter binding in the human brain leading to disturbances in lipid metabolism or neuronal signaling in the CNS. Such effects, if present, are proposed to have significant consequences on synaptic plasticity and membrane remodeling following neuronal injury. Consistent with this possibility, in vitro and animal studies have indicated that apoE3 appears to enhance synaptic plasticity and decrease neurotoxicity compared to apoE4, though there are a few conflicting reports.[9, 57]

In humans, PET studies have revealed that the brains of cognitively normal *APOE ε*4 individuals display reduced cerebral glucose metabolism two decades earlier than the expected mean age of onset for *APOE ε3* homozygousindividuals, [58] consistent with several studies demonstrating that young and elderly *APOE ε*4-carriers exhibit regional glucose hypometabolism compared to non-carriers.[58–59] Interestingly, cerebral glucose hypometabolism is correlated with increase in mid-life serum cholesterol in cognitively normal *APOE ε*4-carriers.[60] Recent fMRI studies reported that brain activity in the default mode network, a brain network spatially overlapping with that of amyloid deposition,[61] is increased in young, middle-aged, and elderly carriers of *APOE ε*4, both with and without amyloid deposition.[62–64] In AD patients, it is unknown whether apoE isoform-specific lipid dysregulation or cellular signaling contributes to cerebral hypometabolism specifically or whether the hypometabolism is secondary to brain injury, altered Aβ metabolism, or other AD-related dysfunction.

ApoE isoform-specific roles in neurotoxicity, independent of interactions with Aβ, may have implications in mechanisms of neurodegeneration in AD.[65] Though most apoE is secreted by glia, neuronal apoE4 secreted in the context of certain models of cellular stress is more sensitive to chymotrypsin-like serine proteolytic cleavage than apoE3,[66] leading to the generation of potentially neurotoxic C-terminal truncated apoE4 fragments. Mouse studies suggest that these fragments lead to neurodegeneration and behavioral deficits through effects on tau phosphorylation and cytoskeletal disruption.[66] In AD patients, C-terminal truncated fragments of apoE are increased relative to normal individuals; however, there are presently no reports of increased C-terminal truncated fragments in *APOE ε*4-positive AD patients. It will be important to determine the overall impact of apoE produced by neurons in neurotoxicity. Since the potential effects of apoE isoforms on lipid metabolism, cell signaling, and neurotoxicity in the CNS have the potential to influence both AD and other neurological disorders, further investigation on this topic is warranted.

Effects of *APOE* genotype on AD therapeutic response

Several AD treatments have been proposed and have been or are being tested in clinical trials. While not all trials have assessed the effect of *APOE* genotype in regard to efficacy and safety, several reports suggest that this could be an important factor in trial design. Three acetylcholinesterase inhibitors (AChE-I), donepezil (Aricept ®), rivastigmine (Exelon®), and galantamine (Reminyl®) are widely used for symptomatic treatment of AD. A recent prospective study in a cohort of mild to moderate AD patients treated with Aricept, Exelon, and Reminyl for 36 weeks found that *APOE ε*4 status did not influence drug efficacy;[67–68] however, previous studies showed that *APOE ε*4-carriers benefit less than non-carriers from treatment with tacrine (Cognex®), an AChE-I.[69–70] A large study of mild cognitive impairment showed that donepezil had a significant effect on delaying progression

from MCI to AD in the first 12 months of the study, but this effect was not observed after 3 years. Secondary analysis showed that the observed effect was more profound among *APOE* ε4-positive than ε4-negative carriers throughout the entire length of the study.[68] However, the benefit observed in *APOE* ε4 carriers may be due not to a biological link between *APOE* and donepezil, but rather the ease in demonstrating the conversion and progression from MCI to AD in *APOE* ε4 carriers compared to non-carriers.

Preliminary clinical trials with Rosiglitazone (RSG), a PPARγ agonist that modulates energy/lipid metabolism and inflammation, demonstrated a significant improvement in cognition in RSG-treated mild to moderate AD patients not carrying copies of *APOE* ε4; however, a decline in cognition in *APOE* ε4-carriers was observed.[71] However, a phase III study later found no significant improvement in cognition in RSG-treated mild to moderate AD patients regardless of *APOE* ε4 genotype.[72]

Active and passive immunizations against soluble or insoluble Aβ in several mouse models of amyloid deposition resulted in reduced amyloid pathology in brain tissue and cerebral vasculature with behavioral improvements in various memory-related tasks.[73–77] A recent phase II passive immunization clinical trial in mild to moderate AD patients with bapineuzumab, a humanized anti-Aβ monoclonal antibody, did not find significant treatment differences in pre-specified within-dose cohort analyses.[78] However, secondary analysis revealed significantly improved clinical outcomes among bapineuzumab-treated patients. By some clinical measures, treatment efficacy was greater in non-carriers of *APOE* ε4 relative to carriers. Importantly, reversible vasogenic edema (VE) was observed in approximately 10% of bapineuzumab-treated patients, the incidence of which was greater in higher dose groups and *APOE* ε4-carriers. Increased vascular amyloid burden, differences in vascular permeability, and increased neuroinflammation in *APOE* ε4-carriers have all been proposed to account for the VE observed in bapineuzumab-treated *APOE* ε4-carriers.[78–80] A recent animal study suggests that the murine version of bapineuzumab can result in rapid inflammatory changes in the brain in areas of amyloid deposition including around CAA.[81] These studies emphasize that drugs designed to alter amyloid load in AD or other neurological disorders may interact with *APOE* genotype, resulting in differential efficacy and outcome. This interaction is an important factor to consider in trial design.

APOE and traumatic brain injury (TBI)

More than a decade of literature has suggested a link between traumatic brain injury (TBI) and AD risk.[82–84] Several groups have reported increased risk for AD in TBI patients carrying an *APOE* ε4 allele,[85–86] an association for which the level of evidence is strong (Table 1). One hypothesis for the increased development of dementia in TBI patients posits that brain trauma precipitates Aβ deposition, a hypothesis substantiated by the increased incidence of Aβ deposition identified in postmortem cortical extracts from acute brain injury patients.[84] The likelihood of identifying Aβ deposits or CAA in postmortem tissue from TBI patients was elevated in *APOE* ε4-carriers relative to non-carriers.[87–88] Given that amyloid deposition is higher in *APOE* ε4-carriers, the interpretation that the brains of *APOE* ε4-carriers may harbor Aβ deposits prior to their acute brain injury remains a formal possibility. Studies using an experimental swine model of diffuse TBI, however, demonstrated the deposition of Aβ following controlled impact.[89–90] A series of studies has also revealed that possession of the *APOE* ε4 allele renders TBI patients more susceptible to poor neurological outcome following brain injury.[91–96] In particular, one prospective cohort study found that TBI patients carrying the *APOE* ε4 allele were twice as likely to suffer poor neurological outcome as non-carriers,[93] an association later found to be most striking in younger patients in a larger cohort.[97] Some discrepancy exists among studies with regard to whether possession of *APOE*ε4 is associated with initial severity of injury versus increased risk of

poor outcome following TBI. However, a recent meta-analysis analyzed 14 prospective TBI studies, concluding that the major effect of *APOE* ε4 was on poor neurological outcome following TBI.[98] Repetitive subacute brain injury commonly results in a progressive disorder known as chronic traumatic encephalopathy (CTE) or the variant, dementia pugilistica (DP), both of which share many of the clinical features of common dementias.[99] Strong associations between *APOE* ε4 and increased risk for CTE and DP have been reported in high exposure football players and boxers.[100–101] Interestingly, in spite of the link between brain injury and increased Aβ accumulation, the brains of patients with these disorders at autopsy also have a significant amount of tau pathology with denser accumulations of tau in more superficial cortical layers than in AD and with not all cases exhibiting increased Aβ deposition.[99] Taken together, these studies strongly suggest a link between *APOE*ε 4 and aberrant Aβ metabolism in the wake of brain injury. In addition, an Aβ-independent process involving tau and other pathways may also be involved in the *APOE* ε4 and TBI connection. Further studies are needed to assess the relative contribution of Aβ, tau, and other mechanisms, in negative outcome following brain injury and the extent to which *APOE* ε4 aggravates pathology.

APOE and Down's syndrome-associated dementia (DAD)

By the age of 40, all individuals with Down's syndrome (DS) develop neuropathological features of AD.[102] Several studies have suggested that the *APOE ε*4 allele predisposes and reduces the age of onset for DAD, while *APOE ε*2 alleles may be protective.[103] One case-control study in a Dutch population reported no effect of *APOE* genotype on incidence or onset of DAD,[103–104] though an early meta-analysis of association studies found that within DS patients, the incidence of dementia was higher in patients carrying *APOE ε*4. A major limitation of these studies has been the relatively small number of patients analyzed. However, a recent longitudinal, large cohort study of DS patients reported that *APOE ε*4-carriers are at higher risk for DAD with earlier onset and accelerated progression compared to non-carriers.[105] Available data suggest that the level of evidence for an association between *APOE ε*4 and DAD is highly suggestive (Table 1).

APOE and outcome after stroke

The observation that *APOE* ε4 associates with poor neurological outcome after TBI has provided the impetus to investigate a possible association between *APOE* and three major pathological types of acute stroke, ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Multiple studies assessing large cohorts of different ethnicities suggest that the outcome of IS in patients carrying the *APOE ε*4 allele is similar to that of non-carriers.[106–108] A recent meta-analysis and several subsequent studies observed an association between *APOE ε*4 and poor neuropsychological outcome after SAH, though there are conflicting reports.[106, 108–110] A similar association was identified in small cohort studies of ICH patients, though *APOE* ε4 also appeared to associate with poor survival in these patients.[111] At present, the level of evidence is suggestive for an association between *APOE* ε4 and ICH and SAH, but not IS (Table 1). It will be critical to employ large cohort studies with standardized follow-up methods to understand whether apoE isoforms play a role in outcome following acute stroke.

APOE and Vascular dementia (VaD)

VaD is the second most common contributor to dementia, accounting for 17–20% of dementia patients in the United States.[112–113] Several studies in multiple ethnicities have shown that possession of *APOE ε*4 increases risk for VaD,[114–116] though an equal number of studies report that *APOE ε*4 does not confer risk.[117–118] Inconsistent results among these studies are likely due to small cohort sizes, misdiagnosis of VaD with AD and mixed

dementia, and lack of population-based, prospective study design. A recent population-based, prospective study following 3424 elderly individuals found that *APOE* ε4 is associated with increased risk for VaD in an allele dose-dependent fashion, with 1.5-fold and 4-fold increased risk for homozygous and heterozygous *APOE* ε4 subjects, respectively (Table 1).[113] While it has been suggested that vascular risk factors like hypertension, diabetes and dyslipidemia are important factors in VaD development,[119] multiple studies suggest VaD risk of *APOE* ε4 is independent of the other vascular risk factors.[113, 120] This may be due to the effect of *APOE* ε4 on concomitant AD pathology contributing to cognitive decline in patients with vascular dementia. Further studies are needed to understand how vascular factors and *APOE* status converge to modulate VaD risk.

APOE and Creutzfeldt-Jakob disease (CJD)

Following a report that apoE immunoreactivity was found in kuru amyloid plaques from CJD patients, an initial study found that the *APOE* ε4 allele frequency of CJD patients did not differ from that of controls.[2] A contradictory report found that the *APOE* ε4 allele associated with definite or probable CJD while *APOE* ε2 decreased CJD-related mortality.[121] Unlike several subsequent studies reporting no such association of *APOE* genotype in several different ethnic populations,[122–124] the Amouyel et al. study analyzed the frequency of allele bearers rather than alleles in addition to including both familial and sporadic CJD patients that were not age-matched with controls. Given the available data, it appears that apoE associates with plaques in CJD patients with no definite role in the disease process (Table 1).

APOE and multiple sclerosis (MS)

Another neurological disorder for which the association of *APOE* genotype and disease is unclear is MS. Though an initial study reported a higher frequency of MS in *APOE* ε4 homozygous individuals from a Danish population,[125] a number of studies have found no association with *APOE* ε4 allele frequency and MS susceptibility.[126] In particular, a meta-analysis of many association studies did not support a role of *APOE* in modulating MS risk, though the effect of population admixture may have limited effect size in the analysis.[126–127] A number of studies support a role of *APOE* ε4 as a progression modifier of MS, having a negative effect on brain pathology, cognitive dysfunction, and severity, though these conclusions are not without controversy.[128] More uniformity in cognitive measures as well as larger studies with longer follow-up in MS patients is needed before conclusions can be drawn regarding the association of *APOE*ε4 and MS progression (Table 1).

APOE and Amyotrophic lateral sclerosis (ALS)

There is a strong consensus among studies that *APOE* genotype is not associated with sporadic or familial ALS risk.[129] However, ample debate exists as to the role of apoE isoforms in differentially modulating age at onset, progression rate, and site of onset in ALS patients. One survival analysis study reported that *APOE* status is not associated with age of onset or site of onset of ALS; however, the progression of the disease appeared to be more rapid in *APOE* ε4-carriers.[130] A family-based association analysis found that *APOE ε2* was protective, resulting in a later disease onset relative to non-carriers; the presence of *APOE* ε4 had no effect on onset despite its suggested role in progression.[131] However, a recent study found an *APOE* ε4 gene dose-dependent association with lower age of onset of sporadic ALS with *APOE* ε4-carriers.[132] Most studies only identify *APOE* as a weak modifier of ALS onset and progression, though additional studies may be needed to clarify the relative effects of *APOE* ε4 and *APOE* ε2 (Table 1).

APOE and Inclusion-body Myositis (IBM)

Several neuropathological features are shared among sporadic and hereditary IBM (s-IBM/h-IBM) and AD.[133] Along with many other proteins, apoE is present in vacuolated muscle fibers of patients with s-IBM and h-IBM,[134–135] prompting groups to assess whether *APOE* genotype is associated with s-IBM/h-IBM. An early study performed in a small cohort of 14 patients reported increased frequency of *APOE* ε4 in s-IBM,[136] but several studies later found no association.[135, 137–138] A recentstudy in a moderately sized cohort of s-IBM patients and a meta-analysis (studies prior to 2007) demonstrated no evidence of risk for s-IBM associated with *APOE* status[139] (Table 1).

APOE and Parkinson's disease (PD)

Clinical and pathological features of PD and AD frequently overlap, leading several groups to investigate the association of *APOE* and PD onset or PD dementia (PDD). The majority of studies have not reported associations between *APOE* ε4 and susceptibility to PD/PDD or age at onset,[140–141] though there are conflicting reports.[142–143] A meta-analysis of 22 studies reported a positive association between the *APOE* ε2 allele frequency and PD risk, while no such association was found in *APOE ε3* or *APOE* ε4 allele carriers.[144] Several reports suggest that *APOE* plays no role in modulating the clinical features of PDD, suggesting that the underlying cause of dementia in PD differs from that of AD.[140, 145] Given that *APOE* ε2 appears to increase PD risk in some studies, it is likely that the role of apoE in PD may be mechanistically distinct from that in other neurological disorders associated with *APOE* ε4 (Table 1).

APOE and Dementia with Lewy Bodies (DLB)

DLB shares clinical and pathological characteristics with both PD and AD.[146] Mounting evidence suggests that *APOE* ε4 is associated with increased risk in DLB, while possession of *APOE* ε2 has no effect.[147–149] This association may be due to *APOE* ε4 increasing the likelihood of Aβ deposition, which is present in many cases of DLB along with synuclein pathology.

Others have reported that *APOE* ε4 does not influence the onset or progression of DLB,[150–151] leaving the association between *APOE* and DLB progression uncertain, given the lack of evidence (Table 1). Interestingly, a recent study in mice overexpressing α-synuclein suggests that apoE might influence the solubility of α-synuclein to influence its aggregation.[152]

APOE and neurological diseases for which association is unclear

Based on associations reported in other neurological diseases, *APOE* has been suggested to play a role in Cerebral Palsy (CP),[153–154] Huntington's disease (HD),[155–156] temporal lobe epilepsy (TL-E), [157–158] and frontotemporal dementia (FTD).[159] However, while some studies have attempted to address a putative association between *APOE* and these diseases, a limited number of studies exist to draw conclusions (Table 1).

There are several possible mechanisms by which *APOE* may influence the onset rate and/or progression of neurological disorders other than AD, CAA, and TBI in which Aβ is not likely to be involved in pathogenesis; however, these mechanisms have not been directly assessed in human studies. Some of the suggested mechanisms, inferred from in vitro and animal studies, by which *APOE* could generally influence neurological disorders are by modulating: (1) neuroinflammation,[160–162] (2) lipid metabolism,[57, 163–165] (3) synaptic plasticity,[166–169] and (4) neuronal toxicity. [66, 170]

Conclusions

Increasing evidence has suggested a central role for apoE in modulating processes of neurodegeneration, particularly in AD and CAA. A large body of evidence has identified *APOE* ε4 as a major AD susceptibility and onset factor, while *APOE* ε2 appears to confer protection (Table 1). A convincing body of literature suggests that *APOE* genotype modulates AD risk largely through its effects on Aβ, probably by influencing aggregation and/or clearance from the brain parenchyma in an isoform-dependent fashion. Epidemiological as well as in vitro and animal studies suggest an Aβ-independent role for apoE which may negatively impact synaptic plasticity, response to neuronal injury, and neuroinflammation. Outcome in neurological disorders such as TBI, hemorrhagic stroke (ICH, SAH), and DAD appear to be influenced by *APOE* genotype. Though associations have been reported between *APOE* and other neurological disorders such as VaD, MS, ALS, PD, and DLB, significant controversy exists among studies with regard to risk, age of onset, and progression. Insufficient data exist to evaluate whether *APOE* genotype associates with risk, age of onset, and progression in CP, HD, TL-E, and FTD. Publication bias and population admixture in meta-analyses, Type I error due to multiple hypothesis testing, and non-uniformity in clinical diagnosis all represent limitations to our current understanding of the association of *APOE* with other neurological diseases. Understanding the detailed mechanism(s) as to how apoE influences Aβ metabolism will be important to better understand AD and CAA pathogenesis and treatment. Further humans studies to understand whether or not apoE plays a role in other neurological diseases are warranted. Emerging evidence suggests that drugs designed for the treatment of neurological disorders have the potential to interact with *APOE* genotype, resulting in differential efficacy and outcome. This interaction may be an important factor to consider in trial design.

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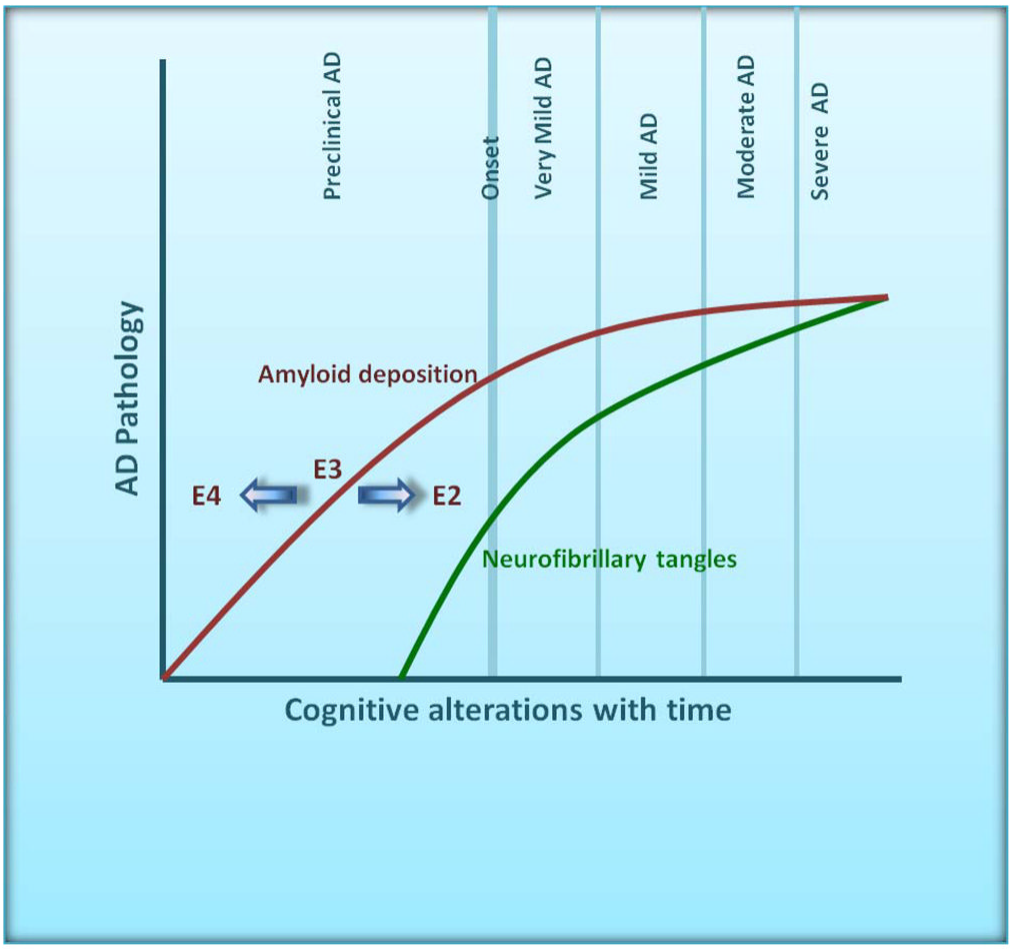

Figure 1.

A large body of evidence suggests that the dominant effect of human apoE isoforms on AD risk is to shift the onset of disease via alterations in the probability of amyloid deposition, likely during the preclinical, asymptomatic phase. Consistent with this hypothesis, individuals appear to accumulate amyloid in the order ε4 > ε3 > ε2, well before AD clinical symptomology becomes manifest (Figure adapted from Holtzman, DM 2008 Nature, 454(7203):418–20)[171].

Table 1

Levels of evidence for an association of *APOE* with occurrence and progression for neurological disorders. Levels of evidence are adapted from the Categories of Association established and used by the Institute of Medicine for association between a factor and a specific health outcome (Committee on Health Effects Associated with Exposures During the Gulf War. Institute of Medicine, 2000) [also see Tarawneh et al., 2010].[172]

Disease	Disease Occurrence and Levels of Evidence	Disease Progression and Levels of Evidence	Possible Mechanisms of ApoE In Disease	References
AD	ε4>ε3>ε2 Sufficient evidence of a direct relationship *(A)*	Inadequate/insufficient evidence to determine whether an association exists *(C)*	• Aβ aggregation and clearance • Tau phosphorylation and aggregation • ApoE protein stability, lipid metabolism, inflammation, altered neuronal repair and synaptic plasticity	1–5,13–24,35–40, 41, 45, 47–57,160–162, 164–170
CAA	ε4>ε3 Sufficient evidence of a direct relationship *(A)* ε2 and ε4 risk for hemorrnage Suggestive evidence of an association *(B)*	ε4>ε3 sufficient evidence of a direct relationship *(A)*	Aβ metabolism	25–34, 38–40, 43, 46, 160–162, 164–170
TBI	Not Applicable	ε4>ε3 Sufficient evidence of a direct relationship *(A)*	Aβ and Tau accumulation	82–101,160–162, 164–170
DAD	ε4> Non-carriers Suggestive evidence of an association *(B)*	ε4> Non-carriers Suggestive evidence of an association *(B)*	Aβ metabolism	102–105, 160–162, 164–170
Stroke (IS, SAH, ICH)	Inadequate/insufficient evidence to determine whether an association exists *(C)*	IS: Inadequate/insufficient evidence to determine whether an association exists *(C)* SAH: ε4 > Non-carriers ICH: ε >Non-carriers suggestive evidence of an association *(B)*	Unclear	106–111, 160–170
VaD	ε4> Non-carriers Suggestive evidence of an association *(B)*	Inadequate/sufficient evidence to determine whether an association exists *(C)*	Unclear	112–120, 160–162, 164–170
CJD	Suggestive evidence of no association *(D)*	Suggestive evidence of no association *(D)*	Not applicable	2, 121–124, 160–162, 164–170
MS	Suggestive evidence of no association *(D)*	ε4> Non-carriers Suggestive evidence of an association *(B)*	Unclear	125–128, 160–162, 164–170
ALS	Suggestive evidence of no association *(D)*	ε4>ε2 Suggestive evidence of an association *(B)*	Unclear	129–132, 160–162, 162–170
IBM	Inadequate/insufficient evidence to determine whether an association exists *(C)*	Inadequate/insufficient evidence to determine whether an association exists *(C)*	Not applicable	133–139, 160–164–170

Disease	Disease Occurrence and Levels of Evidence	Disease Progression and Levels of Evidence	Possible Mechanisms of ApoE In Disease	References
PD	ε2> Non-carriers Suggestive evidence of an association *(B)*	ε2> Non-carriers Suggestive evidence of an association *(B)*	Unclear	140–145, 160–162, 164–170
DLB	ε4> Non-carriers Suggestive evidence of an association *(B)*	Inadequate/insufficient evidence to determine whether an association exists *(C)*	Aβ metabolism	146–152, 160–162, 164–170
CP, HD, FTD, TL-E	Inadequate/insufficient evidence to determine whether an association exists *(C)*	Inadequate/insufficient evidence to determine whether an association exists *(C)*	None proposed	153–159, 162–164, 164–170

(A) Sufficient evidence of a direct relationship: Evidence fulfills the guidelines for sufficient evidence of an association, is supported by experimental data in humans and animals, and satisfies several of the guidelines used to assess causality: strength of association, dose response relationship, and consistency of association.

(B) Suggestive evidence of an association: Evidence is suggestive of an association between *APOE* and the neurological disorder in humans, but the body of evidence is limited by the inability to exclude chance and bias, and confounding factors with confidence.

(C) Inadequate/insufficient evidence to determine whether an association exists: Evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between *APOE* and the neurological disorder in humans.

(D) Suggestive evidence of no association. There are several adequate studies that are consistent in not showing a positive association between *APOE* and the neurological disorder in humans.

Table Abbreviations: AD: Alzheimer's disease; CAA: cerebral amyloid angiopathy; TBI: traumatic brain injury; IS: ischemic stroke, ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; DAD: Down's syndrome-associated dementia; CJD: Creutzfeldt-Jakob disease; MS: multiple sclerosis; ALS: amyotrophic lateral sclerosis; IBM: Inclusion-body myositis; PD: Parkinson's disease; VaD: Vascular dementia; DLB: Dementia with Lewy bodies; CP: cerebral palsy; HD: Huntington's disease; TL-E: temporal lobe-epilepsy; FTD: Frontotemporal dementia