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Multifaceted roles of APOE in Alzheimer disease

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Abstract

For the past three decades, apolipoprotein E (*APOE*) has been known as the single greatest genetic modulator of sporadic Alzheimer disease (AD) risk, influencing both the average age of onset and the lifetime risk of developing AD. The *APOE*ε4 allele significantly increases AD risk, whereas the ε2 allele is protective relative to the most common ε3 allele. However, large differences in effect size exist across ethnoracial groups that are likely to depend on both global genetic ancestry and local genetic ancestry, as well as gene–environment interactions. Although early studies linked APOE to amyloid-β — one of the two culprit aggregation-prone proteins that define AD — in the past decade, mounting work has associated APOE with other neurodegenerative proteinopathies and broader ageing-related brain changes, such as neuroinflammation, energy metabolism failure, loss of myelin integrity and increased blood–brain barrier permeability, with potential implications for longevity and resilience to pathological protein aggregates. Novel mouse models and other technological advances have also enabled a number of therapeutic approaches aimed at either attenuating the *APOE*ε4-linked increased AD risk or enhancing the *APOE*ε2-linked AD protection. This Review summarizes this progress and highlights areas for future research towards the development of APOE-directed therapeutics.

Introduction

Since the identification of the amyloid-β (Aβ) peptide as one of the two culprit aggregation-prone proteins (together with tau) in 1984 (ref. 1), Alzheimer disease (AD) research has matured to the point that disease-modifying drugs that target Aβ are becoming available for clinical use[2–4]. Similarly, since its discovery in 1993 (ref. 5), our understanding of the link between the apolipoprotein E (*APOE*) gene and AD risk has gained exciting momentum. Indeed, in the past decade in particular, we have witnessed unprecedented progress in the

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R.J.J. and A.S.-P. reviewed the literature and wrote the manuscript draft. B.T.H. reviewed and edited the draft.

Competing interests

R.J.J. declares no competing interest. B.T.H. serves on the SAB of Latus and of Dewpoint and has a family member who is employed by Novartis. A.S.-P. has signed a material transfer agreement with Ionis Pharmaceuticals, Inc.

Additional information

areas of APOE-related genetic epidemiology, neuropathology, biomarkers, pathophysiology and therapeutics. Each of these advances has greatly broadened the scope of APOE research from its role in AD to those in AD-related dementias, from its interaction with Aβ to those with tau and other aggregation-prone proteins, and from a mere lipid transport function to complex cell-autonomous and non-autonomous effects involving virtually every brain cell type.

Although early studies linked APOE to Aβ, a mounting body of research has associated APOE with other neurodegenerative proteinopathies as well as with broader ageing-related brain changes, such as neuroinflammation, energy metabolism failure, myelin integrity and blood–brain barrier permeability. Furthermore, evidence has revealed potential implications for *APOE* in longevity and resilience to pathological protein aggregates. This new evidence has also expanded the repertoire of striking differences in behaviour across APOE isoforms, even though they differ in only two amino acid residues. Novel mouse models, gene delivery and silencing and other technological advances have also uncovered a number of approaches by which APOE could be therapeutically targeted.

In this Review, we will summarize the current perspectives on genetic, neuropathological, biomarker, pathophysiological and therapeutic aspects of APOE. First, we provide an update on *APOE* genetics, including the marked changes in *APOE*-linked AD risk driven by genetic ancestry, specific genetic modifiers and certain *APOE* mutations. Then, we cover the neuropathological, biomarker and clinical correlates of the *APOE* genotype and discuss the controversies around direct versus indirect effects of APOE on proteinopathies other than Aβ. Next, we detail the normal structure and function of APOE and the pathophysiological consequences of APOE isoforms with respect to aggregation-prone proteins (Aβ, tau, α-synuclein and TDP-43) and to the function of various brain cell types (astrocytes, microglia, neurons, oligodendrocytes and blood–brain barrier). Finally, we review the main therapeutic approaches tested in mouse models to date and posit that this body of knowledge is mature enough to be leveraged towards the development of disease-modifying drugs with the ultimate goal of preventing and/or slowing down AD progression.

Genetic basis of the APOE locus

The *APOE* gene maps to chromosome 19q33 (Fig. 1) and is part of a cluster of related genes with *APOC1*, *APOC4* and *APOC2*. The *APOE* variant linked with sporadic AD risk is a haplotype consisting of two single-nucleotide polymorphisms (SNPs), rs429358 (T/c, p.C112R) and rs7412 (C/t, p.R158C), which determine a single amino acid substitution — arginine (Arg) or cysteine (Cys) — in positions 112 and 158, resulting in three alleles: ε2 (Cys112, Cys158), ε3 (Cys112, Arg158) and ε4 (Arg112, Arg158). *APOE*ε3 is the most common allele in the general population, representing ~80% of alleles, and is used as reference[5–7]. *APOE*ε4 increases the risk of developing AD, and *APOE*ε2 is protective against developing AD in a dose-dependent fashion, so that *APOE*ε4 homozygotes have the highest risk and the rare *APOE*ε2 homozygotes have the lowest[5,7,8]. Traditionally, *APOE*ε3/ε4 individuals and *APOE*ε4 homozygotes were asserted to have ~2–3 and ~9–12 times higher risk of AD than *APOE*ε3 homozygotes (reference group), respectively, and *APOE*ε2/ε3 carriers were believed to have about half the risk of *APOE*ε3 homozygotes[5,7].

However, the effect size of the *APOE* genotype on AD risk is now known to depend on a number of variables, including demographics such as race and ethnicity, age and sex, and whether the AD diagnosis is made on clinical or neuropathological[8] grounds, or confirmed with biomarkers[9].

Influence of genetic ancestry in *APOE* effects

The classic view of the dose-dependent *APOE*ε4-linked increase in AD risk and *APOE*ε2-linked protection against AD is currently being redefined owing to the application of modern genetic epidemiology methods to large populations of diverse ancestry. The initial intriguing observation that the *APOE*ε4 allele increases AD risk differentially across races and ethnicities, with the greatest increase in risk seen in East Asian people, followed by white, then Black, then Hispanic people[6], has now been confirmed by a larger meta-analysis using not only self-reported race and ethnicity but also global genetic ancestry to ascertain the biological basis of these demographics[10]. In the analysis, *APOE* allele frequencies for East Asian, white, Black and Hispanic people were as follows: *APOE*ε2 carriers 5.6%, 11.1%, 19.7% and 10.6%; *APOE*ε3 homozygotes 72.8%, 50.6%, 43.3% and 61.3% and *APOE*ε4 carriers 21.6%, 40.6%, 41.6% and 29.9%, respectively[10]. Even more puzzling than these differences in *APOE*ε4-linked AD risk are those associated with the *APOE*ε2 allele; this study found that the protective effect of *APOE*ε2 is attenuated in Black versus white people, whereas in Hispanic and East Asian individuals, the *APOE*ε2 allele confers essentially no protection against AD relative to *APOE*ε3 homozygosis, and only in the presence of *APOE*ε4 does *APOE*ε2 confer protection in Hispanic people[10] (Fig. 2).

Deciphering the substrate (substrates) of ethnicity and race-based differences in the odds of developing AD associated with the *APOE* genotype could provide new molecular targets for prevention and therapeutic development. Besides the effects of global genetic ancestry causing variability across the genome — for example, higher Amerindian and African American global ancestry might attenuate *APOE*ε4-linked increased AD risk[10,11] — differences in local ancestry causing genetic variability around the *APOE* locus are a major focus of investigation[12,13]. Interestingly, *APOE* mRNA expression levels seem to be higher in astrocytes from *APOE*ε4 homozygous individuals with European versus African local ancestry[14]; this observation could be owing to substantial differences in the frequency of certain SNPs that impact the regulation of the *APOE* gene expression[15].

Influence of sex and age in *APOE* effects

The odds of AD associated with the *APOE* genotype are not uniform across age or sexes. Rather, age and sex moderate the effects of the *APOE* genotype on AD risk so that the risk associated with the *APOE*ε3/ε4 genotype is highest in women of ages 60–70 years (or 70–80 years according to ref. 6) but decreases in older women and equalizes to that of non-Hispanic White, Black and Hispanic men of the same age[10]. Notably, this age × sex interaction with the *APOE*ε3/ε4 genotype was not only seen in non-Hispanic White people but also replicated in Black and Hispanic individuals via meta-analysis of both groups, suggesting that the interaction is independent of race and ethnicity[10]. This finding has implications for genetic counselling and design of prevention clinical trials. As shown

subsequently, the biological basis of this interaction between *APOE* and both sex and age has begun to be unravelled but remains poorly understood.

Genetic modifiers of *APOE*ε4-linked AD risk

Although *APOE*ε4 homozygosity may approach 100% penetrance for Aβ deposition in the brain[16], even for white or East Asian people, being homozygous for *APOE*ε4 is not synonymous with developing AD dementia; the lifetime risk up to age 80–85 years for mild cognitive impairment or dementia owing to AD has been estimated as 30–55% for *APOE*ε4 homozygotes, 20–25% for *APOE*ε3/ε4 carriers and 10–15% for *APOE*ε3 homozygotes according to population-based studies with a majority of individuals of European ancestry[17,18]. Large meta-analyses of genome-wide association studies (GWAS) have uncovered more than 80 other risk and protective loci[19,20] that could potentially augment or attenuate the *APOE*-linked AD risk. This moderating effect has been elegantly shown by comparing the polygenic risk score (PRS) of a cohort of people homozygous for *APOE*ε4 who either had early-onset (<65 years) AD or were still cognitively unimpaired at age >75 (‘resilient’); the resilient cohort had a much lower PRS than the early-onset cohort[21]. Similarly, individuals with subjective cognitive decline and *APOE*ε4 carriers were more likely to advance to AD dementia if they had a high PRS (calculated without *APOE*), whereas a low PRS attenuated the *APOE*ε4 effect size[22].

Several other SNPs not revealed by GWAS have been shown to attenuate the risk of AD associated with the *APOE*ε4 allele. Of particular interest is the longevity-increasing *KLOTHO*-VS heterozygosity, which has been reported to operate by decreasing Aβ plaque deposition, tau accumulation and tau-mediated cognitive impairment[23–26]. *CASP7* rs10553596 and *SERPINA3* rs4934-A/A have also been suggested to confer resilience against AD in people homozygous for *APOE*ε4 aged >75 years[27].

Non-genetic modifiers of *APOE*ε4-linked AD risk

Besides genetic modifiers, non-genetic acquired factors comprising the AD exposome — for example, education attainment, exercise, diet, cardiovascular risk factors, hearing loss and pollution[28,29] — could also moderate the effect of *APOE* on AD risk and partly explain ethnoracial differences in effect size. Indeed, some studies have suggested an interaction between *APOE* genotype and several of these modifiable risk factors, whereby carrying the *APOE*ε4 allele would multiply the increased AD risk associated with the risk factor alone (for example, cardiovascular risk factors[30]) or counteract the reduced AD risk conferred by a protective factor, such as education attainment[31] or physical exercise[32]. However, not all epidemiological studies have detected these interactions[33]. By contrast, reported estimates of the population attributable fraction of dementia for these modifiable risk factors, meaning the percentage of dementia cases that could be prevented if each factor was eliminated from the population, are higher in Black and Hispanic people than in white and Asian people, which points to complex genome × environment interactions[34,35]. More epidemiological research is needed to confirm these *APOE* gene × environment interactions, and more preclinical studies to dissect the underlying mechanisms.

APOE mutations

Aside from the *APOE*ε2, ε3 and ε4 alleles, several other rare missense variants in the *APOE* gene have been reported to influence AD risk and age of symptom onset (Table 1 and Fig. 1).

R136C (Christchurch). The R136S (Christchurch) mutation has been reported to confer protection against AD on the basis of a unique individual carrying the *PSEN1* E280A mutation who was homozygous for the *APOE*ε3 allele with the R136S mutation[36]. This woman had an expected age of symptom onset of 44 years but did not present with mild cognitive impairment until her 70s and exhibited lower than expected tau PET radiotracer uptake. In addition, the woman had relatively preserved precuneus metabolism shown by ^{18}F-fluoro-deoxy-glucose (FDG)-PET, despite substantial Aβ PET radiotracer uptake and hippocampal atrophy, and at autopsy examination had an atypical distribution of neurofibrillary tangles, with greater density in the occipital cortex than in the frontal cortex and hippocampus[36], suggestive of the posterior cortical atrophy variant of AD.

APOE R136S is a very rare mutation (0.0004% allele frequency in the European population[37]) that was originally described in *APOE*ε2 alleles of people with type III hyperlipoproteinaemia[38,39], but is much more common in *APOE*ε3 homozygotes than in any other genotype and has also been associated with increased plasma apolipoprotein B (APOB) levels[37]. The protective effect of the *APOE* R136S mutation seems to require homozygosis, given that four individuals with *PSEN1*-E280A and heterozygous for *APOE*ε3^{R136S} developed mild cognitive impairment at the expected age of 45 years[36] and some *APOE*ε3^{R136S} heterozygous individuals with autopsy-proven AD had early onset of symptoms[40].

R145C. The R145C mutation has been reported only in the *APOE*ε3 allele in individuals with African ancestry and has been associated with both a ~2–3-fold higher risk of AD and an earlier age of symptom onset in those with the *APOE*ε3^{R145C}/ε4 genotype[41].

V236E (Jacksonville). The V236E (Jacksonville) mutation has been described only in the *APOE*ε3 allele and reduces the risk of AD down to that of *APOE*ε2 carriers or even further[42,43]. This mutation has been associated with a reduction in fibrillar Aβ plaque by amyloid PET and neuropathological examination[44].

Neuropathological correlates of *APOE* genotype in late life

What are the specific neuropathological correlates of the *APOE* genotype? The answer is not straightforward considering the prominent differences in AD risk across genetic ancestries and that most studies addressing this question have been conducted in samples with a majority of non-Hispanic white participants, thus limiting their generalizability to other ethnoracial groups. Although multimodal biofluid and imaging biomarker studies are offering a unique opportunity to study the neuropathological correlates of *APOE* longitudinally in living individuals (Box 1), genetic–neuropathological correlation studies remain insightful, particularly given the frequent finding of multiple potential neuropathological contributors to cognitive impairment, some of which lack

a useful biomarker such as TDP-43 pathology[45]. Thus, next we review our current understanding of *APOE* neuropathological correlates with a special emphasis on non-AD neuropathologies, presenting either comorbid with AD neuropathological changes or as primary neuropathological diagnoses.

APOE and AD neuropathological changes

Relative to the *APOE*ε3 homozygote reference group, carrying one or two *APOE*ε4 alleles is independently associated with a higher Aβ plaque burden and more severe cerebral amyloid angiopathy (CAA), whereas *APOE*ε2/ε2 and ε2/ε3 individuals have fewer Aβ plaques[46–50] but are more likely to have CAA[51]. Of note, although CAA typically affects leptomeningeal and cortical medium- and small-sized arteries, a subtype of capillary CAA has been associated with *APOE*ε4 carriage[51,52]. In contrast to Aβ pathology, the existence of a direct effect of *APOE* genotype on the severity of tau neurofibrillary tangle pathology remains controversial, with most studies agreeing that *APOE*ε4-linked effect on tangles is primarily indirect, mediated through its increase of Aβ plaque burden[46–48,53]. By contrast, *APOE*ε2 has been found to have both direct and indirect (through Aβ) protective effects against tangle pathology[48,49].

The *APOE*ε2/ε4 genotype has been comparatively less studied owing to researchers either including this genotype within the *APOE*ε4^{+} group because of its low frequency or deliberately excluding it to avoid potential confounding of their results by a putative cancellation of the effects of these opposite alleles. However, relative to *APOE*ε3 homozygotes, *APOE*ε2/ε4 carriers have greater Aβ plaque burden[54], increased CAA severity[50] and increased odds of macroinfarcts[55], whereas differences in tangle burden are conflicting[49,54]. Of note, *APOE*ε2/ε4 individuals have a particularly high risk of intracerebral lobar haemorrhage in the presence of CAA[50], possibly because the *APOE*ε2 allele has been associated with fibrinoid necrosis of the vessel wall[56,57]. Overall, these data indicate that the *APOE*ε4 allele is functionally dominant over the *APOE*ε2 allele.

APOE and cerebrovascular diseases comorbid with AD

AD is frequently accompanied by cerebrovascular disease[45,58]. Compared with *APOE*ε3 homozygosis, *APOE*ε4 carriage has been independently associated with increased cerebrovascular burden in the form of gross (macro) infarcts in some studies[55], but not others[50], whereas *APOE*ε2 is associated with more severe ischaemic small vessel disease in the form of arteriolosclerosis, especially in individuals aged 90 years and older[55]. Neither allele is associated with atherosclerosis in the circle of Willis or microinfarcts[55].

APOE and other neurodegenerative diseases comorbid with AD

As with cerebrovascular disease, the co-occurrence of AD with other age-related neurodegenerative proteinopathies such as α-synucleincontaining Lewy bodies and neurites in the neocortex, amygdala and substantia nigra, and TDP-43-containing neuronal cytoplasmic inclusions and dystrophic neurites in the hippocampus and amygdala — the so-called limbic-predominant age-related TDP-43 encephalopathy neuropathological changes or LATE-NC — is not uncommon, and they cooperate to worsen cognition[59–61]. Carriers of the *APOE*ε4 allele have increased odds of a multi-proteinopathy, whereas carrying the

*APOE*ε2 allele reduces these odds, relative to *APOE*ε3 homozygosis[60,61]. Specifically, *APOE*ε4 carriage has been independently associated with increased odds and severity of Lewy body pathology[49,62] and TDP-43 pathology[59,63,64] and with the presence of TDP-43-related hippocampal sclerosis[63] in the scenario of a primary neuropathological diagnosis of AD.

APOE and primary neurodegenerative diagnoses other than AD

Converse to the *APOE*ε4-associated increased likelihood of comorbid proteinopathies in people with AD, the *APOE*ε4 allele also correlates with the presence of AD neuropathological changes in people with a primary neuropathological diagnosis of amyotrophic lateral sclerosis, neocortical Lewy body disease (LBD), primary tauopathies including Pick's disease, progressive supranuclear palsy (PSP) and corticobasal degeneration and multiple system atrophy[65]. However, the association between the *APOE* genotype and 'pure' non-AD primary neuropathological diagnoses in which AD neuropathology is absent or minimal is highly controversial, as discussed subsequently.

Tauopathies. One study found that the *APOE*ε2 allele is associated with increased odds of neuropathologically confirmed primary tauopathy (PSP and corticobasal degeneration)[66]. However, another study failed to find such association[67] and in a third study the significance of the association was lost when adjusting for AD neuropathological changes[49], suggesting a spurious association owing to the strength of the *APOE*ε4–AD link. The first study[66] also found increased numbers of tau inclusions, including oligodendroglial coiled bodies, tufted astrocytes and neuropil threads, and an up-trend for neurofibrillary tangles in *APOE*ε2 carriers with autopsy-proven PSP. Of note, *APOE*ε4 has been associated with greater severity of chronic traumatic encephalopathy[68].

α-Synucleinopathies. *APOE*ε4 has been associated with a faster rate of cognitive decline in people with Parkinson disease, independent of AD neuropathology assessed by levels of CSF biomarkers Aβ42 and pTau[69]. Furthermore, the ε4 allele has been associated with increased risk of a dementia presentation in people with pure α-synucleinopathies[70]. *APOE*ε4 has also been associated with the burden of α-synuclein inclusions in LBD with minimal AD co-pathology[62,71], although other studies have only found an association between *APOE*ε4 and LBD in the presence of AD neuropathology, but not in pure LBD[72,73]. By contrast, no association has been found between the *APOE* genotype and a primary neuropathological diagnosis of multiple system atrophy[67,74].

TDP-43 proteinopathies. An association between the *APOE*ε2 allele and higher levels of TDP-43-positive dystrophic neurites (but not neuronal cytoplasmic inclusions) in the motor cortex of individuals with amyotrophic lateral sclerosis and frontotemporal lobar degeneration-TDP has been reported[75].

Other correlates of *APOE* genotype in late life

Cognitive correlates

The well-established association between *APOE* genotype and cognition — whereby *APOE*ε4 accelerates age-related cognitive decline[76] and *APOE*ε2 delays it[77] — is largely mediated by genotype-specific effects on AD neuropathological changes and, to a lesser extent, on comorbid pathologies[46–48,78,79]. However, after controlling for the presence and severity of AD neuropathology and comorbid pathologies, carrying the *APOE*ε4 allele might still accelerate the rate of cognitive decline in the normal ageing-sporadic AD continuum, whereas carrying the *APOE*ε2 allele might slow down cognitive decline[47,77,80,81]. This observation suggests that *APOE* drives differential neurotoxic effects or neural network vulnerability that is independent of neuropathology severity. Remarkably, *APOE*ε4 can accelerate age-related cognitive decline even in genetically determined AD, such as familial autosomal dominant AD[31] and Down syndrome[82], whereas *APOE*ε2 can delay age of onset even in familial autosomal dominant AD[83].

Cardiovascular risk

APOE genetic variants are known to affect serum cholesterol levels and cardiovascular risk. Indeed, several GWAS have linked the rs4420638 and rs10402271 SNPs of the *APOE–APOC* cluster with higher serum LDL cholesterol levels and an increased risk of coronary artery disease[84,85]. By contrast, *APOE*ε2 has been associated with reduced risk of coronary and carotid artery diseases in diverse populations[86]. In large health registries such as the UK BioBank, the *APOE*ε4 allele has been associated with higher LDL cholesterol and triglycerides levels, lower HDL cholesterol levels and an increased risk of coronary artery disease. By contrast, in the same registries, *APOE*ε2 has been associated with lower LDL cholesterol levels, increased triglyceride levels and increased risk of peripheral vascular disease[87,88]. The rare *APOE*ε2 homozygotes are at increased risk of developing hyperlipoproteinaemia type III (also known as familial dysbetalipoproteinaemia), characterized by very high triglyceride levels[89]. These observations reflect the differential effects of APOE isoforms in lipid metabolism, which will be discussed further in the section ‘Current perspective on APOE pathophysiology’.

Impact on survival versus mortality

Several studies of large populations of individuals from European ancestry have raised the possibility that *APOE* is a longevity gene, with the *APOE*ε2 variant associated with longer survival and the *APOE*ε4 with shorter survival in a dose-dependent manner[90–94]. Of note, contrary to expectation, these associations seem to be independent of baseline serum LDL cholesterol[93], cardiovascular risk[93,94] and even AD diagnosis or the burden of AD neuropathology[94]. Together, these observations argue against underlying competing risks and suggest that as-yet-unknown mechanisms mediate the impact of *APOE* on survival. Conversely, the *APOE*ε4 allele has been proposed to hold evolutionary health benefits earlier in life that might explain its high frequency in the general population (Box 2).

Current perspective on APOE pathophysiology

What is APOE?

APOE is a protein canonically secreted to the extracellular space where it functions as a lipid transporter[95]. In the CNS, APOE is produced predominantly by astrocytes, although it can also be produced by reactive microglia and, to a lesser extent, stressed neurons and other glial cells[96,97]. Lipids are loaded onto APOE via transmembrane ATP-binding cassette (ABC) transporters such as ABCA1 and ABCG1 (ref. 98) (Fig. 2a). The structure of APOE changes markedly upon its binding to lipids to form lipoprotein particles, and the different APOE isoforms are predicted to undergo this change in structure at different rates, which partly influences their affinity for lipoprotein particles of different sizes[99,100].

Cryo-electron microscopy of APOE lipoprotein particles secreted from astrocytes in culture has revealed that APOE forms an anti-parallel dimer that wraps a discoidal lipoparticle in a ‘double-belt’ configuration[101]. APOE3 has a higher affinity for HDL, whereas APOE4 is more likely to bind LDL and VLDL[102]. This difference affects the amount and type of lipids that APOE can deliver within the brain but also changes the affinity of APOE for its various receptors (reviewed elsewhere[103]). Receptor binding is likely to be a key mechanism by which APOE isoforms regulate AD risk, as modulation of these receptors has been shown to affect AD neuropathology[104–108]; however, greater understanding of how this effect occurs is needed.

APOE protein interactions

Amyloid-β. The link between APOE4 and Aβ has been studied extensively for the past three decades, and the interaction between the two proteins has now been established as one of the mechanisms by which the *APOE*ε4 allele increases AD risk[109]. APOE4 is associated with increased Aβ deposition, and the mechanism behind this is multifaceted. Before the seminal genetic studies identifying *APOE*ε4 as a risk factor for AD[5] and *APOE*ε2 as protective[7], APOE was found to co-deposit with both cerebral and systemic amyloid deposits. Thus, APOE was proposed to be acting as a molecular chaperon to promote the seeding and misfolding kinetics of Aβ[110]— a hypothesis that has been supported by more recent work[111]. Indeed, APOE affects the seeding and aggregation of Aβ in an isoform-dependent manner[112], and the increased propensity of Aβ to oligomerize in the presence of APOE4 is considered a major mechanism by which APOE4 increases AD risk[113–116] (Fig. 2c). In several different Aβ plaque-depositing mice that are genetically engineered to express the human APOE isoforms instead of mouse APOE (Box 3), APOE4 induces greater Aβ fibrillization and deposition in compact plaques relative to APOE3, whereas APOE2 markedly delays the onset and decreases the extent of Aβ plaque deposition[117–120]. Moreover, in these mouse models, APOE4 has also been shown to impair Aβ clearance relative to APOE3, with APOE4–Aβ complexes exhibiting a lower binding affinity for APOE receptors, which results in a slower receptor-mediated clearance and a longer half-life of Aβ in *APOE*4 mice[117] (Fig. 2e).

Besides promoting Aβ aggregation and impairing its clearance, APOE isoforms can also differentially influence the transcription of Aβ precursor protein and the generation of

Aβ; these factors are most increased by APOE4, followed by APOE3, then APOE2 (ref. 121). *Apoe* knockout plaque-depositing mice highlight the complexity of the APOE–Aβ interaction, as these mice still exhibit deposition of Aβ plaques, but the plaques are less compact and do not cause the synaptic and cognitive deficits typical of plaque-depositing mice with *Apoe* intact[117,119,122]. These preclinical data, together with a case study of an *APOE* null individual with hyperlipoproteinaemia type III but normal cognition and AD biomarkers[123], indicate that lowering APOE expression levels is a valid therapeutic strategy. However, antisense oligonucleotide therapy in mice suggests that lowering APOE levels is less effective after plaque deposition than before plaque deposition[124], which reinforces the idea that Aβ plaque deposition is a multistep process.

Tau. Although for many years the effects of APOE on tau were assumed to be mediated through Aβ, animal and cell models of tauopathies have revealed that APOE4 is associated with a greater burden of misfolded and hyperphosphorylated tau and more severe tau-induced neurodegeneration, both in the presence and in the absence of Aβ[125,126]. Specifically, in a tauopathy mouse model (PS19, overexpressing the *MAPT* P301S mutation) crossed with *APOE*-targeted replacement mice (Box 3), APOE had a marked isoform-dependent effect on tau pathology in the absence of Aβ plaques, with *APOE*4/PS19 mice showing the greatest extent of tau neurofibrillary tangle pathology and neuronal loss and *APOE*2/PS19 mice the lowest[127] (Fig. 2f). Although the different APOE isoforms did differ in their propensity to induce pTau and tau aggregation, of greater importance was the much higher level of tau-induced neurodegeneration in the *APOE*4/PS19 mice. Importantly, *Apoe* knockout/PS19 mice were relatively spared from any neuronal and hippocampal volume loss when compared with any of the APOE-expressing mice, despite similar levels of tau accumulation compared with *APOE*3/PS19 mice[127]. These results bear a striking resemblance to those from the Aβ plaque-depositing mice[120,128] and indicate that the effect of APOE4 in AD is due not only to the increased propensity of proteins to aggregate in the presence of APOE4, but also to the way APOE4 modulates the brain response to those aggregates once formed. This observation is crucial for therapeutic development as it suggests that targeting APOE holds therapeutic potential despite high aggregate burden, thus after symptom onset in AD. Indeed, mounting evidence shows that APOE downstream effects converge on the microglial response to protein aggregates, as further discussed subsequently[129,130].

α-Synuclein. The strong association between APOE4 and Aβ has overshadowed possible links between APOE and other aggregation-prone proteins. Studies using *APOE*-targeted replacement (*APOE*-TR) mice crossed with mutant α-synuclein (αSyn) mice have reported that *APOE*4 mice have increased aggregation of αSyn, whereas *APOE*2 mice have very limited αSyn aggregates. Furthermore, the *APOE*2 mice have improved motor function and prolonged survival compared with *APOE*3-expressing mice, suggesting that the effect of APOE on α-synucleinopathies is independent of its effect on Aβ[69]. Biochemical studies indicate that APOE4 increases the seeding potential of αSyn[131,132], and further mouse studies have shown that APOE4 alters the proteolytic processing of αSyn. Together, these results highlight again the multifaceted effects of APOE4 on protein aggregation[133]. More studies are required to understand the role of APOE in pure α-synucleinopathies.

TDP-43. As APOE has been shown to exert effects on TDP-43 pathology in post-mortem brains, mouse models might hold the key to understanding the impact of APOE isoforms in this proteinopathy. A study using adeno-associated viral (AAV) vectors to overexpress TDP-43 in the brains of *APOE*-TR mice of all three isoforms and in *Apoe* knockout mice revealed that, surprisingly, *APOE*2-targeted replacement TDP43-overexpressing mice have greater reactive gliosis, neurodegeneration and motor impairments[75], compared with *APOE*3-TR, *APOE*4-TR and *Apoe* knockout mice, which had very mild or no phenotypic alterations. Although this study showed that APOE isoforms can differentially affect TDP-43 pathology in the absence of Aβ, further work is needed to uncover the underlying mechanisms).

Propensity of APOE for aggregation

The differential effect of APOE isoforms on multiple proteins that are prone to pathological misfolding and aggregation in β-pleated sheet-rich fibrils in the brain raises the intriguing possibility that APOE acts as a chaperone of aggregation-prone proteins, with APOE4 having the greatest propensity to facilitate misfolding. Much work has gone into uncovering the mechanisms by which APOE4 might increase the likelihood of pathological misfolding and deposition of aggregation-prone proteins; however, APOE itself has also been shown to form aggregates, particularly in its non-lipidated state[99,134,135] (Fig. 2). Whether these multimers of APOE have a biological function remains to be clarified, but the propensity of APOE, particularly APOE4, to form dimers, tetramers and higher order oligomers in solution has complicated attempts to get an accurate picture of the structure of the protein[99,135].

Intriguingly, the protective *APOE* Jacksonville mutation (Fig. 1) has been found to reduce APOE oligomerization and Aβ deposition, which could point to APOE oligomerization being biologically detrimental and adds weight to the hypothesis that APOE oligomerization might facilitate Aβ oligomerization[44]. Along this line, an antibody against non-lipidated APOE, which is the version most likely to oligomerize, has shown promise in multiple AD mouse models[136–139]. Computational and biochemical work from the past few years has begun to elucidate the molecular underpinnings of APOE multimerization, but greater understanding of how mutations in APOE affect its structure and both receptor- and lipid-binding properties would propel the discovery of APOE-targeted therapeutics aiming to prevent or slow down AD progression[134,140,141].

Cell type-specific effects of APOE

Astrocytes. Astrocytes provide the vast majority of the cholesterol required by mature neurons, and the APOE they produce is crucial for efficient cholesterol transport[142]. Astrocytes derived from *APOE*4 human-inducible pluripotent stem cells (hiPSCs) are less efficient at secreting lipidated APOE particles and exhibit impaired cholesterol metabolism relative to *APOE*3 hiPSC-derived astrocytes[143,144]. This impairment is likely to be detrimental first to astrocytes and, secondarily, to neurons and could ‘prime’ the brain for neurodegeneration[145]. *APOE*4 astrocytes have an increased number of lipid droplets and impaired glucose utilization and mitochondrial function, lending further support to this hypothesis[143,146,147] (Fig. 2b).

Given that astrocytes are the primary producers of APOE in the brain, the cell-autonomous and non-autonomous effects downstream of astrocytic APOE production have received considerable attention. To study such effects, novel mouse models have been developed that enable the removal of the *APOE*4 or *APOE*3 genes selectively from the astrocytes of *APOE* knock-in mice (see 'CureAlz' *APOE* mice, Box 3). These studies have revealed that removal of both astrocytic APOE3 and APOE4 is protective against Aβ deposition in plaque-depositing mice; specifically, plaque burden was lowered to the levels of *Apoe* knockout mice[148]. However, only astrocytic *APOE*4 deletion, but not *APOE*3 deletion, significantly ameliorated tau neurofibrillary tangle burden in tauopathy mice[149]. Interestingly, these studies found that removal of astrocytic APOE reduced microglial reaction to Aβ plaques and neurofibrillary tangles, but that astrocyte response to plaques and tangles was largely unchanged[148,149], suggesting 'paracrine' effects of astrocytic APOE on microglia and supporting the idea that APOE is essential in astrocyte–microglia crosstalk.

Microglia. Although APOE is predominantly produced by astrocytes in the healthy brain, its expression is markedly upregulated by reactive microglia in the brains of individuals with AD[96,150]. This upregulation is a key element of a conserved transcriptional signature of reactive microglia that has been found in multiple neurodegenerative diseases[150,151]. Together with triggering receptor expressed on myeloid cells 2 (TREM2), APOE has also been shown to regulate microglial response to Aβ plaques and neurofibrillary tangles in AD as well as in other neurodegenerative diseases[150]. This so-called disease-associated microglial (DAM) response is differentially regulated by the various APOE isoforms, probably through their differential binding to specific surface microglial receptors such as TREM2 (refs. 152,153) (Fig. 2d). Reactive microglia migrate towards Aβ plaques, surround them and upregulate APOE, which binds to TREM2 and promotes plaque compaction[154]. This process is likely to explain why both *Apoe* knockout and *Trem2* knockout plaque-depositing mice exhibit reduced microglial reactivity against Aβ plaques and their plaques are less compact[117,119,122,155]. Importantly, this *APOE–TREM2* axis has also been found in transcriptomic post-mortem analyses of human brains, with *APOE*ε4 carriers exhibiting a more prominent pro-inflammatory and phagocytic microglial transcriptomic signature[152,153]. Moreover, evidence shows that this microglia-derived APOE has distinct post-translational modifications when compared with APOE produced by astrocytes and this, too, is isoform-dependent[156].

Although this body of evidence has led many to propose that microglia-derived APOE upregulates the DAM response in a cell-autonomous manner, new studies draw a more complex picture. In contrast to complete *Apoe* knockout mice, microglia-specific *Apoe* knockout Aβ plaque-depositing mice (Box 3) exhibit largely unchanged microglial and Aβ phenotypes except for slightly larger plaques[157]. By contrast, removing *APOE*4 specifically from microglia of *APOE*4/PS19 tauopathy mice rescued a neuroprotective microglial signature[157,158]. Additionally, as mentioned earlier, the characterization of microglia in astrocyte-specific *Apoe* knockout mice certainly indicates that microglia are affected by astrocytic APOE[148,149]. Furthermore, *APOE*4 microglia-like hiPSCs show decreased phagocytosis and increased inflammatory genes relative to *APOE*3 microglia[143]. In summary, data from the past 5 years on novel mouse models support a complex interplay

among microglia, astrocytes and AD neuropathology, but more research is needed to fully understand this complexity.

Neurons. Similar to microglia, neurons produce APOE in times of stress, albeit to a lesser extent[96]. The characterization of hIPSC-derived neurons indicates that neuronal APOE4 is associated with altered synaptic function, fatty acid accumulation and hyperexcitability[143]. Mouse models expressing *APOE*3 or *APOE*4 exclusively in either astrocytes or neurons (Box 3) show that APOE3 from both cell types can protect against neuronal hyperexcitability, whereas neuron-derived (but not astrocyte-derived) APOE4 is detrimental[159,160]. A separate study has shown that removing APOE4 from neurons in a tauopathy mouse model leads to a significant reduction in tau neurofibrillary tangle pathology and tau-induced neurodegeneration[161]. This work highlights the important role of neuron-derived APOE and underscores the need for a deeper understanding of the ways in which APOE differs on the basis of the source cell type.

Oligodendrocytes. Post-mortem analysis of brain tissue has shown an association between the *APOE*ε4 allele and a reduced number of oligodendrocytes in the frontal cortex after controlling for the severity of AD neuropathology[162]. Moreover, studies performed in post-mortem brain tissue and in vivo using *APOE* knock-in mouse models have all associated *APOE*4 with impaired myelination of oligodendrocytes resulting from altered cholesterol transport[163,164]. These studies indicate that cholesterol transport is impaired both within oligodendrocytes[163] and from astrocytes to oligodendrocytes[164]. Interestingly, *Apoe* knockout mice and LDL receptor (*Ldlr*)-overexpressing mice — which display low levels of APOE owing to internalization and clearance of APOE lipoproteins — have larger pools of oligodendrocyte progenitor cells and increased myelin coverage of axons, supporting the idea that APOE regulates oligodendrocyte number and function[106].

APOE and cellular metabolism

The brain, and particularly its neurons, are energetically very demanding, and the regulation of both cellular lipid content and mitochondrial function is essential for brain health. In vitro studies have shown that fragments of APOE, which are more abundant with APOE4 than with APOE3, can cause neuronal mitochondrial dysfunction[165,166]. Further, in vitro studies have indicated that this mitochondrial dysfunction partly results from a blockade of mitophagy owing to APOE4-mediated lysosomal dysfunction, which leads to an accumulation of damaged and dysfunctional mitochondrial in APOE4 carriers[167–169]. In addition, in both a mouse model and human postmortem brains, *APOE*ε4 is linked to altered expression of proteins involved in mitochondrial fission and fusion, suggesting that an alteration in mitochondrial dynamics might lead to or arise from impaired mitochondrial function[147,170].

Mitochondria have a key role in buffering and storage of calcium ions, which is crucial for the correct functioning of neurons[171,172]. Impaired calcium flux has been observed in vitro in an APOE4-expressing neuronal cell line compared with an APOE3-expressing line and could be partially responsible for the hyperexcitability seen in *APOE*4 neurons in culture[173].

*APOE*4-TR mice exhibit multiple alterations of energy metabolism compared with *APOE*3-TR mice, including impaired mitochondrial respiration in the cortex and hippocampus, upregulation of oxidative phosphorylation genes in the entorhinal cortex and differential levels of fatty acids and other metabolites[174]. In particular, *APOE*4 astrocytes and microglia have increased glycolytic activity when compared with the same cells expressing *APOE*3 (refs. 175,176). Neurons shuttle fatty acids to glial cells via APOE, with APOE4 being less efficient than APOE3 at this transport[177]. Glial cells then store excess free fatty acids in the form of triglycerides and cholesterol esters in intracellular lipid droplets, which serve as an energy storage until they are catabolized in mitochondria via β-oxidation, and this process is compromised in the presence of APOE4 (refs. 146,177) (Fig. 2b). Work both in vitro and in vivo has highlighted an APOE isoform-specific impact on lipid droplet accumulation in astrocytes[146], neurons[177] and microglia[178]. Notably, in 1907, Alois Alzheimer described an accumulation of lipid droplets in astrocytes around senile plaques[179].

Intriguingly, not only has APOE been shown to affect mitochondrial structure and function, but also mitochondrial dysfunction has been shown to impact APOE gene and protein expression and secretion[180].

APOE and the brain vasculature

APOE circulating in the blood is predominantly produced by the liver; however, the BBB keeps this pool of peripheral APOE separated from that produced in the CNS[181,182]. Nevertheless, peripheral APOE seems to influence the brain partly by impacting the BBB. When compared with wild-type mice, both *Apoe* knockout mice and mice expressing *APOE*4 have a leaky BBB, a phenomenon also reported in cognitively unimpaired and mildly impaired individuals who carry an *APOE*ε4 allele[183–185]. These observations have led to the hypothesis that *APOE*4 constitutes a loss-of-function APOE variant with respect to BBB maintenance. Indeed, when *APOE*4 was knocked out from astrocytes, the BBB was able to repair itself, indicating that APOE4 produced by astrocytes is responsible for this BBB leakage[184]. A leaky BBB increases plasma proteins in the brain parenchyma, thereby leading to oxidative stress and neuroinflammation, and is yet another mechanism by which APOE could prime the brain for neurodegeneration[145]. Intriguingly, removal of APOE4 specifically from astrocytes of *APOE*4 knock-in plaque-depositing mice leads to increased CAA but also increased BBB integrity, indicating that APOE4 itself could be more deleterious for BBB integrity than the vascular Aβ build-up[186] (Fig. 2g).

Besides BBB integrity, APOE4 has a negative impact on cerebral blood flow and neurovascular coupling; *APOE*4 mice show reduced cerebral blood flow both at baseline and in stimulus-evoked paradigms, relative to *APOE*3 mice[187–189]. Moreover, APOE4 also reduces the density of blood vessels in these mice, thereby potentially impairing oxygen availability to neurons[188]. Importantly, the development of anti-Aβ immunotherapies has encountered a major roadblock precisely in the propensity of *APOE*ε4 carriers to BBB leakage: although the FDA-approved anti-Aβ monoclonal antibodies are very effective at removing Aβ from the brain parenchyma, a substantial proportion of treated individuals, especially *APOE*ε4 carriers, exhibit amyloid-related imaging abnormalities (ARIA) consisting of oedema (ARIA-E) and haemosiderin deposits (ARIA-H)[2]. The risk

of developing these potentially serious adverse effects is higher in *APOE*ε4 carriers, particularly homozygotes, and current recommendations are that patients are genotyped for *APOE* before starting these therapies to offer a balanced benefit–risk discussion[190].

APOE-targeted therapeutics

Given the high *APOE*ε4 allele frequency and large effect size with respect to AD risk (at least in populations of European and East Asian ancestry), as well as all its deleterious consequences on brain homeostasis listed earlier, in 2024 a consensus panel[191] concluded that lowering APOE4 levels is a reasonable approach to prevent or slow down AD progression. This and other therapeutic strategies targeting APOE that have been explored to date are summarized next.

Blocking APOE interactions

APOE4 is associated with increased oligomerization and deposition of Aβ in vitro and in vivo[113,115,192], so blocking the interaction between Aβ and APOE is a promising strategy to mitigate the facilitation of Aβ seeding and aggregation by APOE4. In mouse models, this has been achieved using a small molecule mimetic homologous to the domain of Aβ that interacts with APOE but is modified to be more protease-resistant. This small peptide can reduce the oligomerization of Aβ in vitro and ameliorate Aβ and tau pathology in a triple transgenic mouse model of AD[193,194] (Fig. 3a). On the inverse of Aβ mimetics are APOE mimetics, in particular, small peptides homologous to the receptor-binding region of APOE. Such APOE mimetics have been shown to prevent microglial reaction in vitro, as well as Aβ deposition and associated memory deficits in *APOE*4 plaque-depositing mice[195,196]. These preclinical findings indicate that mimetic peptides designed to prevent APOE binding to either Aβ or APOE receptors could be therapeutically viable.

Initial in vitro functional experiments with the *APOE* Christchurch protective mutation (see the section ‘R136C (Christchurch)’) suggest that this mutation weakens the interaction between APOE and heparan sulfate proteoglycans — located on the surface of neurons and implicated in tau uptake — and, therefore, that blocking APOE–heparan sulfate proteoglycan binding might have therapeutic value[36] (Fig. 3a). This prediction was confirmed in vivo in 2023 by two studies that used mouse models expressing human *APOE*3 or *APOE*4 with the Christchurch mutation, which showed amelioration of AD phenotypes when compared with *APOE*3 or *APOE*4 mice, particularly those related to tau accumulation and microglial response[197,198]. Moreover, an APOE Christchurch-mimetic antibody that disrupts APOE–heparin binding has shown promise in reducing tau hyperphosphorylation in mouse models of tauopathy[199].

Increasing APOE2 levels

Gene therapy has already been efficacious in other neurodegenerative diseases, most notably spinal muscular atrophy[200,201]. Multiple laboratories are pursuing the development of gene therapy approaches to express *APOE*2 in an *APOE*4 background. The introduction of human *APOE*2 into plaque-depositing mice expressing endogenous mouse *Apoe* via AAV-mediated delivery was shown to prevent and even reverse the deposition of Aβ into plaques, whereas

delivery of *APOE*4 had the opposite effect[128] (Fig. 3b). Furthermore, in mice, administration of APOE2 was found to be beneficial at reducing plaque deposition even in the presence of APOE4, indicating that APOE2 can reduce some of the negative effects of APOE4 (refs. 202,203). Remarkably, the first human trial using AAV to express *APOE*2 in *APOE*ε4 homozygotes has been initiated, and the reported safety results from this phase I trial are promising despite the small number of participants[204] (NCT03634007).

Decreasing APOE4 levels

Immunotherapy using anti-APOE antibodies is another way of lowering APOE4 levels in the brain. An antibody that preferentially binds to non-lipidated APOE4 has shown promise in reducing Aβ plaques and CAA in a mouse model of β-amyloidosis, as well as decreasing Aβ-driven tau seeding in mice[137–139]. Targeting of the non-lipidated version of APOE4 is predicted to be more successful than targeting the lipidated version, as non-lipidated APOE is more likely to co-deposit with Aβ plaques and also to self-associate[139] (Fig. 3c). However, as with most immunotherapies, stimulating microglia via their Fc domain could potentially have undesired detrimental effects on the brain[139,205].

Another mechanism of decreasing APOE4 expression is using antisense oligonucleotides against APOE4 (Fig. 3d). This method has been effective in mouse models of both Aβ plaque deposition and tauopathy, although the timing of administration seems to be crucial for success[124,206]. For example, starting before Aβ plaque deposition prevented Aβ plaque development, whereas animals treated after the onset of plaque deposition actually showed an increase in Aβ plaque size and plaque-associated dystrophic neurites. These results indicate that clinical trials with these therapeutics should be carefully designed[124].

Increasing APOE lipidation

Aside from the aforementioned immunotherapy against specifically non-lipidated APOE, efforts are also being made to increase the extent of APOE lipidation without directly affecting APOE levels. Liver X receptors and retinoid X receptors are known to increase APOE lipidation[207,208]. Bexarotene is an FDA-approved liver X receptor/retinoid X receptor agonist for use in refractory cutaneous T cell lymphoma and has been shown to enhance Aβ clearance and improve cognitive performance in plaque-depositing mouse models[209]. However, in phase Ib and II trials, bexarotene increased cerebrospinal fluid APOE by only 25% and failed to reduce PET Aβ burden or alter brain Aβ metabolism, probably owing to poor BBB penetration, although it caused hyperlipidaemia in most participants[210,211]. More recently, peptide mimetics used to upregulate ABCA1 were shown to increase APOE4 lipidation and reduce Aβ deposition and cognitive deficits in *APOE*4 knock-in (but not *APOE*3 knock-in) plaque-depositing mice, indicating that directly targeting APOE lipidation is an effective therapeutic approach[212] (Fig. 3e).

Correcting APOE4 conformation

The single amino acid changes in the different APOE isoforms result in slightly different structures, which have a strikingly large effect on the binding affinities of APOE to lipids, Aβ and receptors[99,111,116,140]. Multiple small molecules have been designed to ‘correct’ the conformation of APOE4 so that it resembles that of APOE3 or APOE2 (refs. 213–217) (Fig.

3f). Some of these molecules have been shown to be effective in cell models, whereas others are in even earlier stages of development[216,217].

Concluding remarks and future directions

APOE continues to be the strongest contributor to AD heritability, despite the discovery of more than 80 risk loci in large GWAS over the past few years[20]. In the past three decades, the field has seen tremendous progress in the understanding of the role of APOE in AD and other neurodegenerative diseases. Technological advances, including bioinformatics approaches applied to big data such as massive electronic health records and multi-omics datasets, cutting-edge structural protein biology methods such as cryo-electron microscopy and novel conditional mouse models, will soon expand our insights on several areas of research priority: first, the genetic and environmental modifiers of *APOE*-linked AD risk, including the genetic modifiers and gene × environment interactions underlying the dramatic differences in AD risk observed across ethnoracial groups; second, the dynamic complexity of APOE 3D structure and its interaction with both lipid cargo and biological receptors, as well as its role as chaperon of aggregation-prone proteins such as Aβ; third, the impact that APOE isoforms, mutations and post-translational modifications (for example, glycosylation) have on APOE 3D structure and interactions; and finally, the cell-autonomous and non-autonomous effects of each APOE isoform in each brain cell type before and after widespread neuropathology. This knowledge could ultimately translate into much needed effective therapies to prevent AD and/or slow down its clinical progression.

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Glossary

Adeno-associated viral vectors
Small non-pathogenic viruses that can infect cells and deliver a small single-stranded DNA cargo of <5 kb. This DNA is then transcribed and translated by the target cell generating the protein of interest.

Antisense oligonucleotides
(ASOs). ASOs are short RNA transcripts that are synthesized to be complementary to the sequence of a specific RNA target with the goals of preventing its translation into the protein and promoting its degradation. ASOs are often chemically modified to increase stability (resistance to degradation by RNAse enzymes) and enhance cellular uptake.

ATP-binding cassette (ABC) transporters such as ABCA1 and ABCG
Transmembrane proteins that transport cholesterol and phospholipids out of the cell to lipid-poor apolipoproteins such as APOE.

Cell-autonomous and non-autonomous

Cell-autonomous effects are those that a perturbed cell exerts on itself or other cells of the same type. Cell-non-autonomous effects are those that a perturbed cell type (for example, astrocytes) exerts on other cell types (for example, microglia), either directly or via its secretome.

Exposome
Set of non-genetic risk factors that can impact the risk of developing certain disease (for example, cancer or Alzheimer disease) of an individual, including cumulative lifetime environ mental exposures and lifestyle habits.

Global genetic ancestry
Genetic variability across the genome that determines the race and ethnicity of an individual based on the relative proportions of various population ancestries (for example, European, African, Amerindian or East Asian), not always coincident with self-reported categories.

Human-inducible pluripotent stem cells
(hiPSCs). Cells derived from skin or blood cells after reprogramming them back to a pluripotent embryonic-like state, which can be then differentiated to recapitulate any main brain cell type, although often embryonic or fetal in nature. Isogenic versions that are genetically identical except for the gene of interest (for example, *APOE*) can be generated with CRISPR–Cas9 technology.

Local genetic ancestry
Genetic variability surrounding a specific locus in the genome of an individual, which can include zero, one or two copies of an allele from each ancestral population, thereby affecting the expression of a gene of interest (for example, *APOE*).

Polygenic risk score
(PRS). An estimate of the genetic relative risk of an individual to develop a certain disease, calculated by applying the summary statistics from meta-analysis of genome-wide association studies involving thousands of cases and controls to the genetic variants of that particular individual.

Triggering receptor expressed on myeloid cells 2
(TREM2). A receptor expressed on the cell surface of immune cells, including microglia, that activates phagocytosis in response to extracellular stress signals (for example, Aβ) through the TYROBP–DAP12 signalling pathway.

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Box 1 |

Biomarker correlates of the *APOE* genotype

Alzheimer disease (AD)

- *APOEε*4 carriers show higher PET amyloid-β (Aβ) burden than non-carriers across the normal ageing–AD dementia continuum[227–229].
- The *APOE*ε2 allele is protective against Aβ plaque deposition: cognitively unimpaired *APOE*ε2/ε4 carriers have lower PET Aβ plaque burden than age-matched *APOE*ε3/ε4 participants[229,230].
- *APOE*ε4 and *APOE*ε2 carriers have a greater and lower PET tau accumulation, respectively, than *APOE*ε3 homozygotes after adjusting for PET Aβ plaque burden, supporting a direct impact of the *APOE* genotype on tau neurofibrillary tangle pathology[231–235].
- In cerebrospinal fluid (CSF), Aβ levels are lower in ε4 carriers and higher in ε2 carriers; total tau or pTau levels are unaffected by the *APOE* genotype[236].

Cerebral amyloid angiopathy (CAA)

- *APOE*ε4 carriers are more likely to exhibit MRI biomarkers of CAA, such as lobar cerebral microbleeds[237,238] and cortical superficial siderosis, than *APOE*ε3 homozygotes[239].
- The *APOE*ε2 allele correlates with cortical superficial siderosis, possibly owing to its vasculopathic effects[56,239].
- The *APOE*ε4 allele is over-represented in people with CAA-related inflammation, a rare entity in which autoimmune humoral and cellular responses to Aβ-laden arterioles lead to brain oedema presenting with encephalopathy, headaches and seizures[240,241].

Neurodegeneration

- Cognitively unimpaired *APOE*ε4 carriers have lower cortical glucose metabolism by ^{18}F-fluoro-deoxy-glucose-PET[242–246] and higher neurofilament light-chain plasma levels[246] than non-carriers, but these associations are likely to be dependent on *APOE* genotype effects on Aβ plaque and tau burdens[247].
- Cognitively unimpaired *APOE*ε2/ε3 heterozygotes and *APOE*ε2 homozygotes have greater grey matter volume than *APOE*ε3 homozygotes in areas typically affected by AD neuropathology, suggesting resilience[248].
- The CSF synaptic markers SNAP-25 (ref. 249) and neurogranin[250] are elevated in *APOE*ε4 carriers with normal cognition and mild cognitive impairment, respectively, compared with non-carriers, suggesting early synaptic loss.

- SNAP-25 was elevated even in amyloid PET-negative individuals[249], whereas neurogranin was not significantly associated with the APOE genotype after controlling for CSF Aβ and pTau levels[250].

Neuroinflammation

- Translocator protein (TSPO) PET imaging shows more neuroinflammation in *APOE*ε4 carriers than non-carriers independently of PET global Aβ plaque and local tau burdens[251].

Reactive astrogliosis

- Neither plasma nor CSF glial fibrillary acidic protein levels differ according to *APOE*ε4 status when adjusting for PET Aβ plaque burden and clinical status[252].
- Plasma glial fibrillary acidic protein levels correlate with PET Aβ plaque burden independently of *APOE* genotype[253].
- Myoinositol levels measured by MR spectroscopy as a proxy for astrocyte function correlate with PET Aβ plaque and, to a lesser extent, tau burden only in APOEε4 carriers, and partly mediate the effect of Aβ on tau[253].

Myelin integrity

- MRI in cognitively unimpaired individuals suggests that *APOE*ε4 might accelerate age-related loss of myelin brain content[254,255].

Blood–brain barrier (BBB) damage

- Dynamic contrast-enhanced MRI shows BBB breakdown in cognitively unimpaired and mildly impaired APOEε4 carriers relative to *APOE*ε3 homozygotes, especially in the medial temporal lobe.
- Cognitively unimpaired and mildly impaired *APOE*ε4 carriers have increased CSF levels of platelet-derived growth factor receptor β, albumin quotient, cyclophilin A and matrix metalloproteinase 9 (ref. 185), indicative of pericyte degeneration and BBB permeability. However, larger studies have failed to detect an independent association between *APOE* genotype and CSF/plasma albumin quotient[256,257] or CSF platelet-derived growth factor receptor-β levels[257] and instead have implicated diabetes[256], dementia (regardless of clinical type)[256], age[257] or reactive astrogliosis[257] in BBB damage.

Box 2 |

Possible evolutionary benefits of *APOEε4* in early life

The high frequency of *APOEε4* in the general population contrasts with all its deleterious consequences in late life. It has been proposed that *APOEε4* is the ancestral variant and that the *APOEε3* and *APOEε2* alleles arose around 200,000–300,000 years ago[258–260]. Given that genetic variants are preserved or extinguished by the pressure of natural selection and *APOEε4* is so deleterious later in life, researchers have asked what evolutionary benefits might be associated with *APOEε4* carriage earlier in life. In evolutionary genetics, this concept is called antagonistic pleiotropy. Invoked advantages of the *APOEε4* allele include enhanced innate immunity to fight childhood enteric infections[261]; improved fecundity and fertility[262]; reduced incidence and aggressiveness of melanoma[263] and other cancers; and even a cognitive edge over young adult *APOEε3* homozygotes in some cognitive tasks, such as short-term memory for brief periods[264], visual search and attention control[265–267], visual working memory[268] and tasks requiring high-demand cognitive control[269]. More evidence is needed to support this hypothesis including large population-based birth cohort studies, ideally complemented with electronic health records and with fluid and imaging biomarkers.

Box 3 |

Mouse models to study APOE

APOE-targeted replacement mice

Endogenous mouse *Apoe* was replaced with human *APOE* with a mouse line for each isoform. This model has been crossed with both Aβ plaque-depositing and tauopathy models[270–272].

APOE knock-in mice (MODEL-AD and JAX)

The mouse *Apoe* gene was humanized through homologous recombination to generate an *APOE*4 knock-in line, whereas the other two *APOE* isoforms were generated by applying CRISPR–Cas9 editing to this original *APOE4* line[273].

APOE knock-in floxed mice (CureAlz)

The mouse *Apoe* gene was replaced with one of the three human *APOE* alleles flanked by loxP sites, which enable the conditional removal of *APOE* upon *Cre* recombinase expression[181]. These mice have been crossed with constitutive and inducible mouse lines expressing Cre in various cell types, namely, astrocytes and microglia, and the resulting mice have been crossed with Aβ plaque-depositing and tauopathy models. *APOE*3 and *APOE*4 Christchurch mice have been generated by introducing the R136S mutation within *APOE*3 or *APOE*4 using a CRISPR–Cas9 knock-in strategy[197,198].

Apoe knockout mice

The endogenous mouse *Apoe* gene was inactivated by homologous recombination and insertion of a neomycin cassette[274]. These mice have been crossed with Aβ plaque-depositing and tauopathy models.

Mice with cell type-specific *APOE* expression

These mice express an *APOE*3 or *APOE*4 minigene specifically in neurons under the control of the neuron-specific enolase promotor, or in astrocytes under the glial fibrillary acidic protein promotor[275,276].

APOE-inducible mice

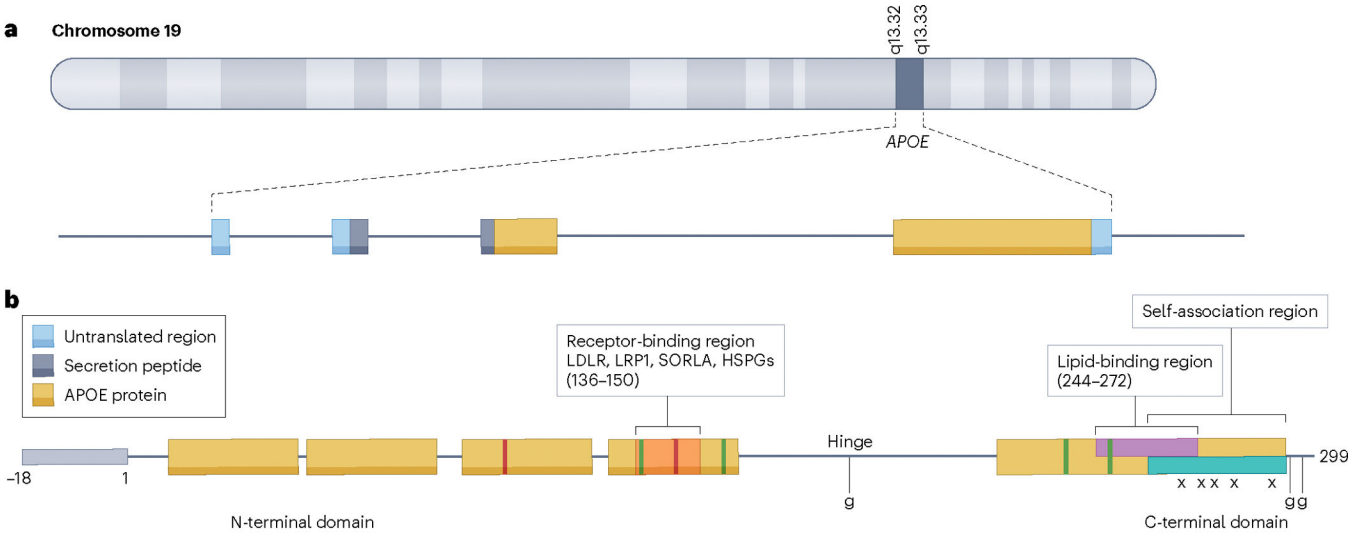
These mice express *APOE*3 or *APOE*4 exclusively in cells expressing *Cre* recombinase upon treatment with oral doxycycline112. The inserted cassette also contains enhanced green fluorescent protein. These mice have been crossed to various *Cre* lines as well as Aβ plaque-depositing mice.

APOE switch mice

These mice express APOE4 until their *Cre* recombinase excises *APOE*4, causing a switch to expression of APOE2 (ref. 277). They have been crossed to diferent *Cre* lines as well as Aβ plaque-depositing mice.

Key points

- The risk of Alzheimer disease associated with the *APOE* genotype is modulated by global and local genetic ancestries, other genetic risk loci and the lifetime exposome of an individual.
- *APOE* missense mutations are providing key insights into the pathophysiology of the classic three APOE isoforms.
- The *APOE* genotype might modulate the risk of other neurodegenerative diseases by influencing the pathobiology of their culprit aggregation-prone proteins.
- The *APOE* isoforms affect a wide range of molecular and cellular functions in multiple brain cell types via cell-autonomous and non-autonomous mechanisms.
- Several strategies to target APOE therapeutically have shown efficacy in preclinical studies and hold promise for translation into clinical trials.



c

		112	136	145	158	236	251
Common variants	*APOE2*	C	R	R	**C**	V	R
	APOE3	C	R	R	R	V	R
	APOE4	**R**	R	R	R	V	R
Rare variants	*APOE3–Christchurch*	C	**S**	R	C	V	R
	APOE3–R145C	C	R	**C**	R	V	R
	APOE3–Jacksonville	C	R	R	R	**E**	R
	APOE4–R251G	**R**	R	R	R	V	**G**

Fig. 1 |. Schematic illustration of structural and functional regions of APOE.

a, The *APOE* gene is located on chromosome 19 at position q13.3 and is transcribed into four exons[218]. **b**, Apolipoprotein E (APOE) is activated after the cleavage of an 18 amino acid secretion peptide and consists of an N-terminal domain comprising four bundled α-helices and a helical C-terminal domain separated by a flexible hinge region[219]. The N-terminal domain contains the receptor-binding region as well as the polymorphisms that differentiate the common APOE isoforms. The C-terminal domain contains the lipid-binding region and a self-associate region that required five mutations (each denoted with an X) to allow the protein to be crystallized[135]. APOE isoforms are differentially *O*-linked glycosylated and the main sites are indicated[220]. **c**, The positions of residues that modify Alzheimer disease risk in the three *APOE* haplotype common variants and in the rarer missense mutations are indicated with red lines for deleterious mutations (text highlighted in red) and green lines for protective mutations (text highlighted in green). HSPG, heparan sulfate proteoglycan.

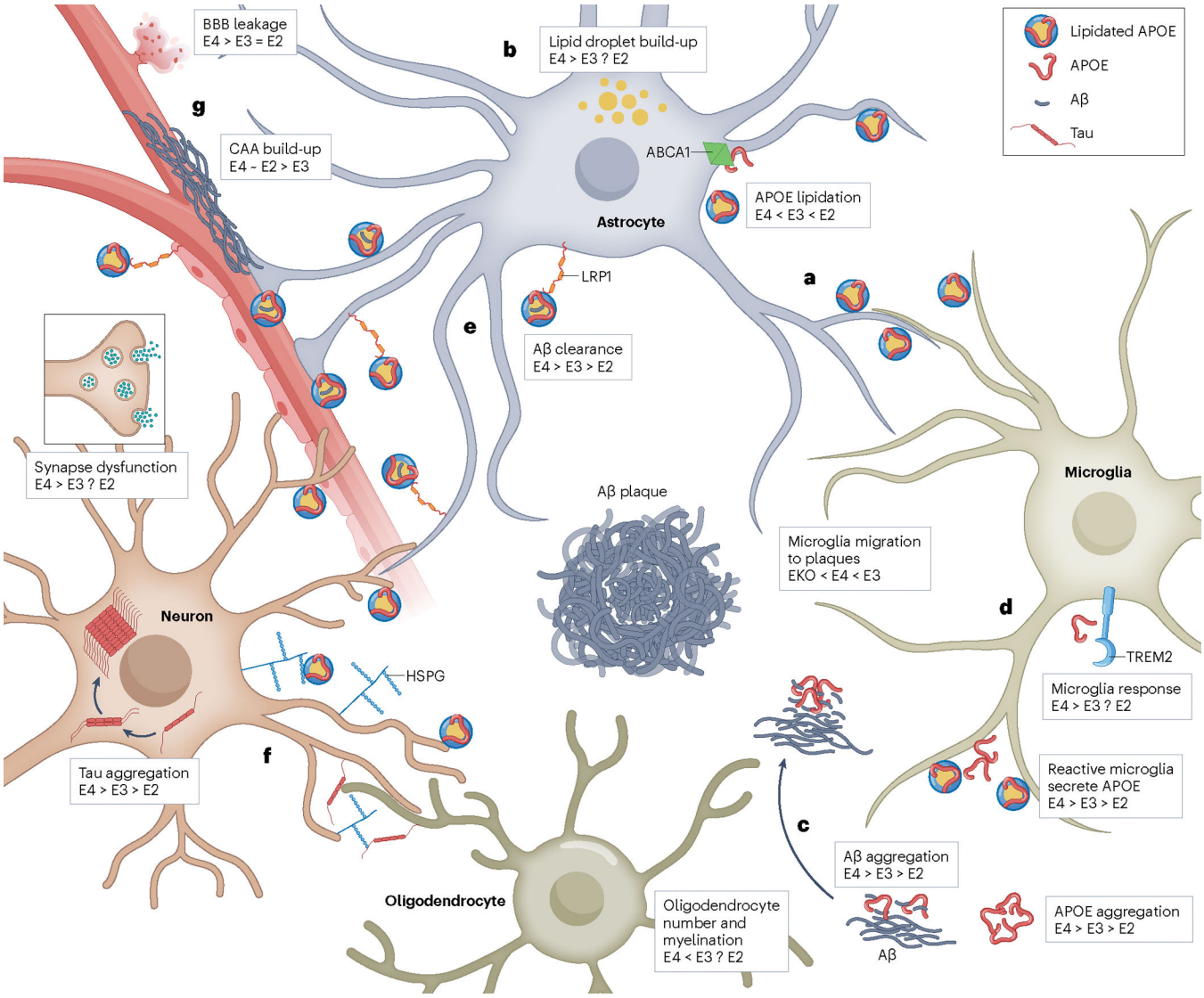


Fig. 2 |. Multifaceted roles of APOE in Alzheimer disease pathophysiology.

Apolipoprotein E (APOE) is produced mainly by astrocytes in the healthy brain but also by reactive microglia in the brains of people with Alzheimer disease[96]. **a**, APOE is lipidated mainly by the lipid transporter ABCA1, which is located in the astrocyte plasma membrane[221]. **b**, APOE4 promotes the accumulation of lipid droplets in the astrocyte cytoplasm, which is indicative of impaired astrocyte lipid transport and energy metabolism[222]. **c**, APOE interacts with the amyloid-β (Aβ) peptide, with APOE4 promoting its oligomerization, fibrillization and seeding into Aβ plaques[113,115,192] and increasing cerebral amyloid angiopathy (CAA)[48]. **d**, APOE interacts with TREM2 in the microglia plasma membrane and affects microglial responses to Aβ and tau (for example, microglial migration to the plaques) in an isoform-dependent manner[150,154,223]. **e**, APOE is internalized by astrocytes, neurons and endothelial cells via LRP1-mediated endocytosis, which has also been implicated in tau uptake by neurons[224,225]. **f**, Extracellular tau and APOE might compete for binding to heparan sulfate proteoglycans (HSPGs) on the neuron

surface, with potential implications for tau propagation[199,226]. **g**, Besides CAA, APOE4 promotes blood–brain barrier (BBB) disruption and both leakage of plasma proteins and microbleeds[183,185]. E4, *APOE*4; E3, *APOE*3; E2, *APOE*2; EKO, *APOE* knockout; '?' indicates phenomenon has either not been studied in *APOE*2 or reports are contradictory.

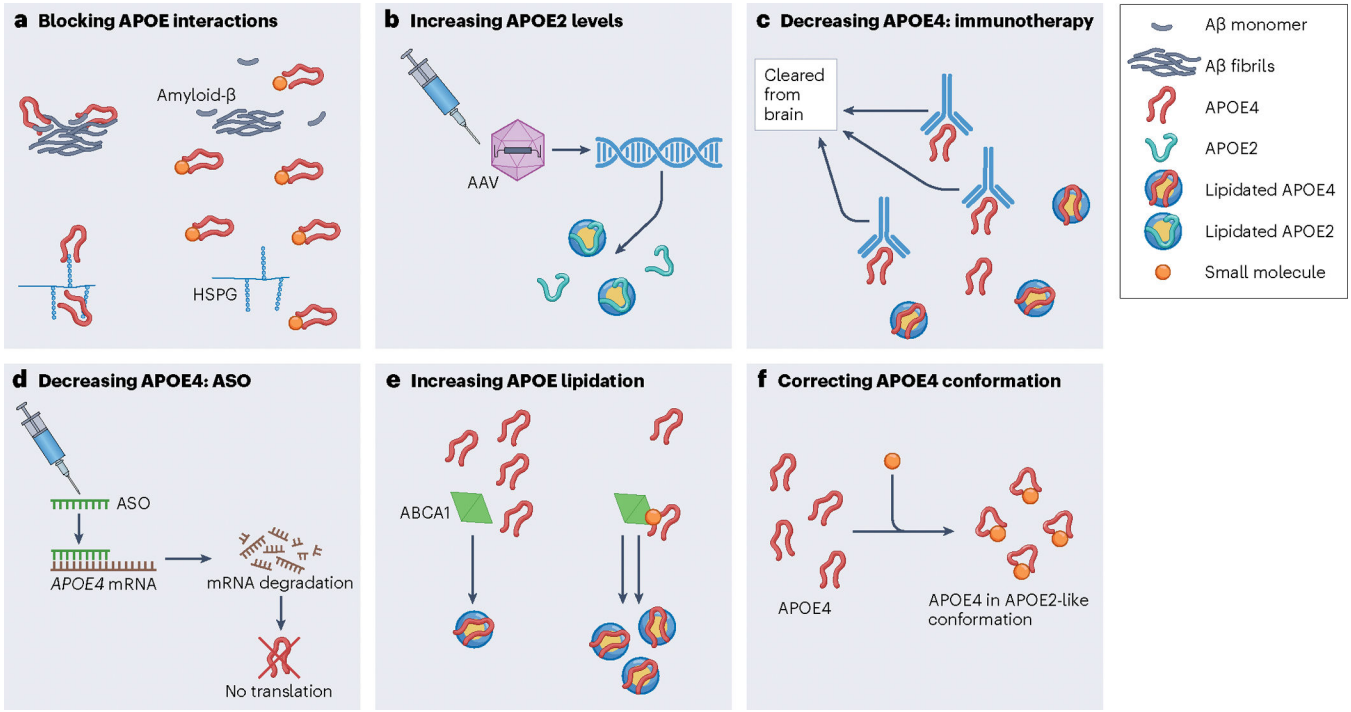


Fig. 3 |. Therapeutic approaches targeting APOE.

Schematic illustrates the main therapeutic strategies targeting apolipoprotein E (APOE) that have been tested in mouse models. a, Blocking APOE interactions using small molecule mimetics of the amyloid p (Ap)-APOE binding domains[193,194]. b, Increasing APOE2 levels via adeno-associated viral (AAV) vector delivery of *APOE2* (refs. 202,203). **c**, Decreasing APOE4 levels using anti-APOE antibodies **d**, Decreasing APOE4 levels using antisense oligonucleotides (ASOs)[206]. **e**, Increasing APOE lipidation by upregulation of ABCA1 with small molecule peptide mimetics[212]. **f**, Using small molecules to correct APOE4 conformation so that it resembles APOE2 (refs. 213,216). HSPG, heparan sulfate proteoglycan.

Table 1 |

APOE mutations that affect Alzheimer disease risk

APOE alteration	*APOE* haplotype	SNP	Amino acid substitution	Major/minor allele	Non-stratified analyses[a]		Stratified analyses[b]		Reference
					OR (95% CI)	*P* value	OR (95% CI)	*P* value	
R136S (Christchurch)	*APOE*ε3	rs121918393	Arg→Ser	C/a	NA	NA	NA	NA	Arboleda-Velasquez et al.36
R145C	*APOE*ε3	rs769455	Arg→Cys	C/t	NA	NA	2.75 (1.84–4.11)	8.3×10^{-7}	Le Guen et al.41
V236E (Jacksonville)	*APOE*ε3	rs199768005	Val→Glu	T/a	NA	NA	0.10 (0.02–0.35)	2.16×10^{-3}	Medway et al.42
					0.37 (0.25–0.56)	1.9×10^{-6}	0.43 (0.27–0.69)	4.4×10^{-4}	Le Guen et al.43
R251G	*APOE*ε4	rs267606661	Arg→Gly	C/g	0.44 (0.33–0.59)	4.7×10^{-8}	0.41 (0.29–0.57)	3.2×10^{-7}	Le Guen et al.43

NA, not available.

[a]Compared with all *APOE* alleles.

[b]Compared with specific *APOE* genotypes: *APOE*ε3 R145C in *APOE*ε3/ε4 versus *APOE*ε2/ε3 + *APOE*ε3/ε3 + *APOE*ε3/ε4; *APOE*ε3 V236E versus *APOE*ε3/ε3; *APOE*ε4 R251G versus *APOE*ε3/ε4.