NEURODEGENERATION

An Alzheimer's-disease-protective *APOE* mutation

Homozygous APOE3-Christchurch (R136S) mutation protects a presenilin 1 (*PSEN1*) mutation carrier from developing Alzheimer's disease until her seventies.

Kelly A. Zalocusky, Maxine R. Nelson and Yadong Huang

Alzheimer's disease (AD) is thought to be caused by complex interactions among multiple genetic, epigenetic and environmental factors. Mutations in three genes—*APP* (encoding amyloid protein precursor), *PSEN1* (encoding presenilin 1) and *PSEN2*—cause early-onset autosomal-dominant AD (ADAD)[1]. PSEN1 and PSEN2 proteolytically process APP to generate various amyloid-beta (Aβ) peptides and other APP cleavage products in the brain[1]. Mutations in the three genes affect APP processing, altering the production of the different Aβ peptides and, thus, their relative concentrations and their propensity to aggregate. Together, these changes lead to increased amyloid plaque formation in the brains of individuals with ADAD[1]. It has been widely suggested that elevated levels of Aβ, Aβ aggregates or amyloid plaques lead to tau protein pathologies and subsequently to AD-related cognitive decline (Fig. 1, left). Apolipoprotein E, whose primary function is to transport lipids in peripheral tissues and in the brain, has three common isoforms: APOE2, APOE3 and APOE4. APOE4 is linked to familial and sporadic late-onset AD; it gene-dose-dependently increases the risk of developing AD and lowers the age of disease onset in carriers[1]. It is also reported to increase Aβ/amyloid accumulation and exacerbate tau pathology (Fig. 1, left)[1].

The world's largest known family of individuals with ADAD, the Colombian PSEN1-E280A mutation carriers, comprises over 1,200 patients[2]. Like other *PSEN1* mutations, the PSEN1-E280A mutation increases Aβ production, leading to amyloid accumulation in the brain. In this kindred, although there is some variability in age of onset and disease progression, both male and female carriers of the mutation have a remarkably fast and consistent disease course, developing mild cognitive impairment and dementia at the median ages of 44 (95% CI, 43–45) and 49 (95% CI, 49–50) years, respectively[3]. Identification of gene variants capable of protecting PSEN1-E280A mutation carriers from developing early-onset ADAD is of fundamental importance for better understanding AD pathogenesis and for developing strategies to treat or prevent AD. In this issue, Arboleda-Velasquez et al. report the identification of a homozygous *APOE* mutation, APOE3-Christchurch (R136S), that conferred strong protection against the development of ADAD in a PSEN1-E280A carrier (Fig. 1, right)[4], opening a promising new avenue in AD research and therapeutics.

The authors identified a PSEN1-E280A carrier who did not develop mild cognitive impairment until her seventies, three decades after the expected age of clinical onset. She also presented with two copies of the exceedingly rare R136S mutation on the *APOE3* background, which the authors suggest is responsible for her resilience to the highly ADAD-penetrant familial

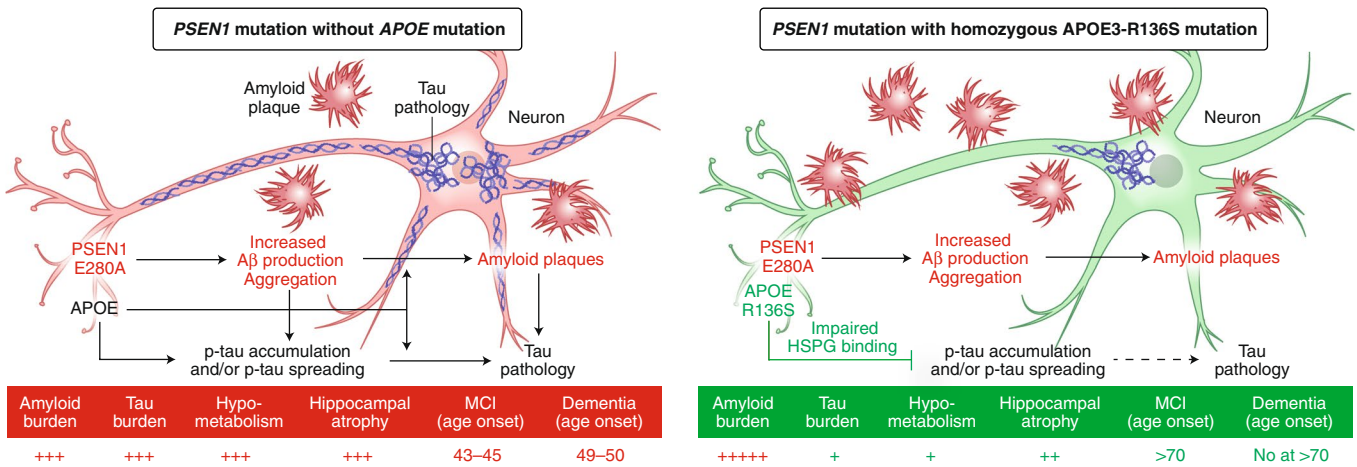

Fig. 1 | Effects of APOE3-R136S on Aβ and tau pathologies, neurodegeneration and cognition in *PSEN1* mutation carriers, with potential underlying mechanisms. Left, summary of brain imaging and clinical assessments of young patients with mild cognitive impairment (MCI) and *PSEN1* mutation and the widely discussed interactive roles of Aβ, APOE and tau in AD pathogenesis. Right, summary of brain imaging and clinical assessments of an aged patient with MCI, *PSEN1* mutation and a homozygous APOE3-R136S mutation, with the potential underlying mechanisms of AD-protective effects of APOE3-R136S in ADAD. p-tau, phosphorylated tau.

PSEN1 mutation. The authors found that this individual had an unusually high brain amyloid burden compared to other PSEN1-E280A carriers, but only limited amounts of tau tangles or other neurodegenerative signs detectable by brain imaging, including AD-associated signatures of cerebral hypometabolism and hippocampal atrophy (Fig. 1, right). Thus, this case illustrates a clear dissociation of Aβ/amyloid accumulation from the tau pathology, neurodegeneration and early cognitive decline typical of carriers of ADAD-causing *PSEN1* mutations.

As mentioned above, a dominant theory in AD research has been that increased Aβ levels, Aβ aggregates or amyloid plaques lead to tau pathologies and subsequently to AD-related cognitive decline (Fig. 1, left). Clearly, the new findings do not support this widely discussed hypothesis. Indeed, the study provides direct evidence that Aβ/amyloid accumulation alone is not sufficient to cause AD, at least in a *PSEN1* mutation carrier with exceedingly high Aβ plaque burden. Alternatively, Aβ might induce tau pathologies and cognitive decline only in the presence of normally functional APOE. Further understanding of this chain of causality will be vital for better understanding AD pathogenesis and improving drug development.

The new findings indicate that the AD-protective effect of the APOE3-R136S mutation may be realized through mechanisms that limit tau pathology and neurodegeneration in the presence of high Aβ/amyloid accumulation (Fig. 1, right). The authors note that the APOE3-R136S mutation affects a region of APOE known to play a key role in binding to lipoprotein receptors, such as the low-density lipoprotein receptor (LDLR), and to heparan sulfate proteoglycans (HSPG)[5]. Importantly, HSPGs are reported to promote neuronal uptake of extracellular tau[6], potentially exacerbating tau spreading and pathologies. The authors' own analysis showed that APOE3-R136S has markedly lower binding affinity for heparin than any of the three common APOE isoforms, including APOE2. Expanding on these observations, the authors generated an antibody against the R136S region of APOE and found that it could both successfully bind APOE3 and reduce its heparin-binding capacity. On the basis of these data, the authors hypothesize that antibodies or other molecules that modulate APOE-HSPG interaction might reproduce the AD-protective effect of APOE3-R136S, including its potential to inhibit tau spreading (Fig. 1, right). This theory warrants experimental testing in cells and animals and, if successful, further clinical studies in humans.

This study makes important strides in addressing several questions that have been debated in the APOE and AD field for decades. In the quarter-century since the C112R mutation of *APOE*[1,5], which gives rise to the APOE4 isoform, was first identified as the major genetic risk factor for AD[7], its incomplete penetrance has led many to regard it as a modifier rather than a causative factor in AD. This new study demonstrates, for the first time, that functional APOE is truly required for full pathological and clinical development of AD, at least in ADAD with massive amyloid plaque burden. In addition, it has been debated whether APOE4 and the AD-protective isoform APOE2 modulate AD pathogenesis through loss-of-function effects or through gain-of-toxicity effects[8,9]. This study suggests that the loss of receptor- and/or HSPG-binding function of APOE3-R136S, also seen to varying degrees with APOE2, is AD protective, indirectly supporting the likelihood that APOE4 has a gain-of-toxicity effect in AD pathogenesis[9]. Finally, this study supports the idea that lowering rather than increasing APOE level could be an effective strategy to treat or prevent AD, regardless of APOE isoform[1,9,10].

Some caution should be taken, however, in interpreting and generalizing the findings from this study, as it reports only one case of the homozygous APOE3-R136S mutation. More clinical cases and/or experimental animal studies are needed to confirm these observations and to explore the underlying molecular and cellular mechanisms. Additionally, although the homozygous APOE-R136S mutation is a strong candidate for the cause of the AD resistance observed in this case, additional work is required to confirm that this homozygous mutation is indeed required for the AD-protective effect. Given that only four APOE3-R136S heterozygotes who also carry the PSEN1-E280A mutation have been identified in the Colombian kindred, epidemiological studies including more individuals heterozygous for APOE3-R136S and/or experimental cell and animal studies are needed to further clarify the heterozygous mutation's effect in AD.

In addition to its clear promise for addressing ADAD, this study raises the important question of whether the R136S mutation would confer a protective effect against APOE4-related late-onset AD. APOE4, the greatest genetic risk factor for this much more common form of AD, has been shown to have both gain-of-toxicity effects[9] and greater heparin-binding affinity compared to the other APOE isoforms[4], suggesting that introducing the R136S mutation may protect against APOE4's pathogenic effects. Because the APOE-R136S mutation is extremely rare in humans, generating mouse models and human induced pluripotent stem cell lines with the mutation in an APOE4, APOE3 or APOE2 background by gene editing would be reasonable next steps to capitalize on this exciting finding for more detailed mechanistic studies related to late-onset AD protection and drug development.

Clearly, this important study, describing a case of remarkable resilience to highly penetrant ADAD, has crucial implications for the role of APOE in AD pathogenesis and treatment. Undoubtedly, this work opens exciting new avenues in AD research and reveals promising possibilities for potential AD therapeutics. ❐

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Competing interests

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