Neurodegenerative disease

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APOE4 homozygosity is a new genetic form of Alzheimer's disease

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New data confirm that *APOE4* homozygosity is a major genetic cause of Alzheimer's disease, warranting the development of specialized research strategies, treatment approaches and clinical trials.

The complexity and multifactorial nature of Alzheimer's disease poses unique challenges for designing mechanistic and clinical studies and for developing therapies[1,2]. Genetically, mutations in three genes—amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) cause early-onset autosomal dominant Alzheimer's disease[1,2] (ADAD), and triplication of the *APP* gene in Down syndrome leads to Down syndrome-associated Alzheimer's disease[3] (DSAD). Notably however, these genetic forms of Alzheimer's disease account for a very small portion of cases of Alzheimer's disease.

Sporadic late-onset Alzheimer's disease accounts for most cases of Alzheimer's disease worldwide, and apolipoprotein E4 (encoded by *APOE4*, a variant of the *APOE* gene) has been considered the strongest genetic risk factor for this form of Alzheimer's disease[4–6]. Although it has been known for some time that *APOE4* homozygosity confers a very high risk of developing Alzheimer's disease[4–6] (with an odds ratio greater than 12), there has been a lack of detailed studies in large cohorts of *APOE4* homozygotes to faithfully determine the role of this genotype in Alzheimer's disease development. In this issue of *Nature Medicine*, Fortea et al.[7] provide comprehensive evidence to support the reconceptualization of *APOE4* homozygosity as a form of genetically determined Alzheimer's disease, like ADAD and DSAD (Fig. 1).

The authors analysed a large pathological dataset from the National Alzheimer's Coordinating Center in the USA (N = 3,297, including 273 *APOE4* homozygotes) and five other clinical datasets from multicenter cohorts with Alzheimer's disease biomarker data from three countries (N = 10,039, including 519 *APOE4* homozygotes). They show that across both sexes, *APOE4* homozygotes fulfill the three main characteristics that define a genetic form of Alzheimer's disease—that is, a near-full penetrance, predictability of the age of symptom onset, and a predictable sequence of biomarker changes[7] (Fig. 1). Notably, the predictability of symptom onset (occurring at 65.1 years, with a 95% prediction interval of 48.5–81.5 years) and the sequence of biomarker changes in *APOE4* homozygotes are very similar to those of the ADAD and DSAD groups[7]. The authors conclude that Alzheimer's disease in *APOE4* homozygotes should be redefined as a genetic form of the disease, similar to ADAD and DSAD. Additionally, through further examination of *APOE3*/*APOE4* heterozygotes, the authors confirmed an autosomal semi-dominant effect of *APOE4* (as reported previously[8]), revealing a distinct *APOE4* gene dosage effect on the pathology, symptom onset and sequence of biomarker changes, with *APOE4* heterozygotes consistently showing intermediate outcomes compared with *APOE4* and *APOE3* homozygotes[7].

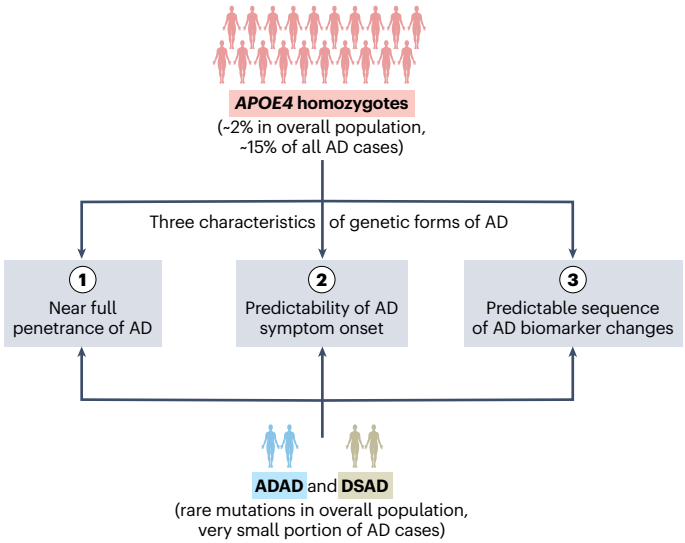

Fig. 1 | Defining genetic forms of Alzheimer's disease. *APOE4* homozygotes account for around 2% of the overall population and 15% of all cases of Alzheimer's disease (AD)[5]. *APOE4* homozygosity should be redefined as a genetic form of Alzheimer's disease—similar to ADAD, which is caused by genetic mutations in *APP*, *PSEN1* or *PSEN2* genes[1,2] leading to altered production of the different amyloid-β peptides and amyloid plaque formation, and DSAD, which is caused by triplication of the *APP* gene[3].

Redefining *APOE4* homozygosity as a genetic form of Alzheimer's disease will have a substantial effect on Alzheimer's disease diagnosis, research and therapeutic development. First, given that the global average proportion[9] of *APOE4* homozygotes is around 2%, the genetic form of *APOE4*-homozygous Alzheimer's disease is likely to represent one of the most frequently occurring Mendelian diseases worldwide. This fact could not only enhance public awareness of Alzheimer's disease, but could also prompt pivotal changes in diagnosis, management of, and care strategies for Alzheimer's disease. This would also be crucial information for individuals who are homozygous for *APOE4* and could motivate the development of educational and counseling programs to support these individuals.

Second, redefining *APOE4* homozygosity as a genetic form of Alzheimer's disease would greatly affect how researchers think about and study Alzheimer's disease. This new definition establishes *APOE4* as a causal factor instead of a risk factor for Alzheimer's disease, emphasizing the need to understand how *APOE4* may initiate and drive Alzheimer's disease pathogenesis. Notably, the potential role of APOE4 in initiating Alzheimer's disease pathways is consistent with

previous observations of a protective effect of *APOE4* deficiency on Alzheimer's disease phenotypes, including both amyloid-β and tau pathologies, in humans and in a human neuron model[10,11]. This also aligns with a 'cell-type-specific APOE4 cascade model' of Alzheimer's disease that proposes that APOE4 — especially neuronal APOE4 — is a crucial pathological initiator and driver of Alzheimer's disease pathogenesis during aging[6,12]. In designing Alzheimer's disease studies, researchers may also consider incorporating homozygous human *APOE4* knock-in mice, especially those with human *APP* and/or expressing human tau, as these would better model the *APOE4* form of Alzheimer's disease.

Third, redefining *APOE4* homozygosity as a genetic form of Alzheimer's disease underscores the urgent need for targeted drug development focused directly on *APOE4*. Although the Alzheimer's disease field has recently expanded beyond amyloid-β-centric therapies to encompass multiple targets, such as tau and neuroinflammation, there has been limited emphasis on *APOE4*-related drug development[6]. The findings of this study should motivate drug developers to prioritize *APOE4* as a therapeutic target. Furthermore, this study also lays a solid genetic foundation for exploring CRISPR-based gene therapies and cell replacement therapies based on human induced pluripotent stem cells that are specifically tailored for patients with *APOE4*-homozygous Alzheimer's disease[6].

Finally, as suggested by the authors, reclassifying *APOE4* homozygosity as a genetic form of Alzheimer's disease would have an important influence on the design of clinical trials. So far, *APOE4* homozygotes have not been treated as a separate predefined treatment group in clinical trials. Following this study, *APOE4* status must be recognized as a crucial parameter in trial design, patient recruitment and data analysis, with *APOE4* homozygotes and heterozygotes being clearly separated. Such an approach may enhance the treatment efficacy and help tailor therapeutic interventions more effectively towards genetically defined patient populations.

Although the findings of Fortea et al.[7] offer substantial insights into the relatively common form of APOE4-homozygous Alzheimer's disease, the authors acknowledge the need for additional longitudinal clinical studies across diverse ethnic groups. As the prevalence of the *APOE4* genotype and the associated risk may vary based on ethnic background[5,9], future investigations should aim to replicate these findings in broader and more diverse populations. Additionally, applying a more comprehensive biomarker panel that incorporates neuroinflammation, alterations in brain activity and especially *APOE4*-related markers[1,6,12] (such as APOE4 fragments) could further elucidate the roles of APOE4 in Alzheimer's disease development. Finally, defining Alzheimer's disease based on pathology and biomarkers according to the AT(N) framework (which incorporates amyloid, tau and neurodegeneration, as done in Fortea et al.[7]) rather than by clinical diagnosis could classify some elderly *APOE4* homozygotes (older than 85 years of age) without clinical dementia as part of the Alzheimer's disease group (although such cases are uncommon). Identifying such individuals who are resistant to the detrimental effects of *APOE4* homozygosity on cognition in the context of severe Alzheimer's disease pathologies would be highly valuable for studying the underlying mechanisms and for developing therapies.

In summary, the timely and pivotal study from Fortea et al.[7], which identifies *APOE4* homozygosity as a major genetic form of Alzheimer's disease, has critical implications in the Alzheimer's disease field. It undoubtedly opens exciting new avenues in *APOE4*-related Alzheimer's disease research, therapeutic development and clinical trial design.

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Competing interests

Y.H. is a co-founder and scientific advisory board member of GABAeron, Inc. The other authors declare no competing interests.