Study suggests two copies of APOE4 gene behind up to 20% of Alzheimer's cases

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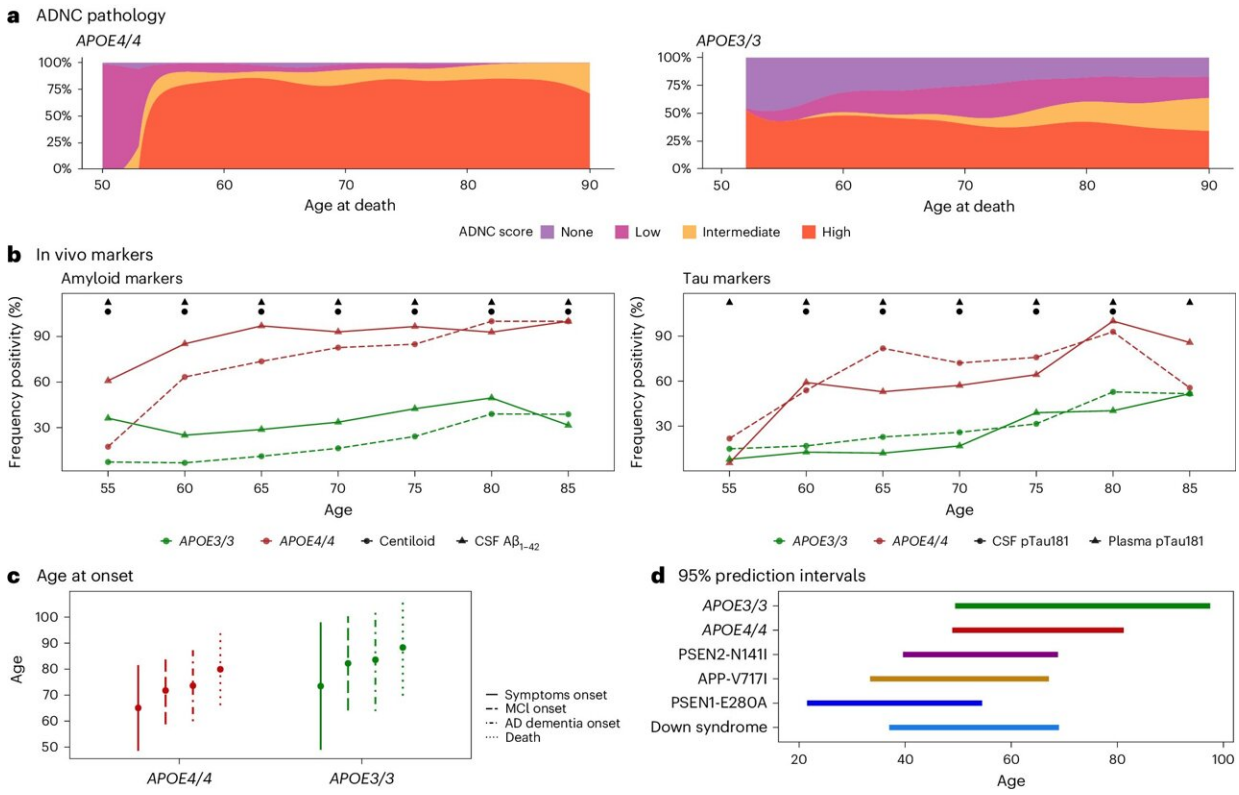

Penetrance and predictive value of APOE4 homozygosity in AD. a, Distribution of ADNC scores by age of death. b, Frequency of positive amyloid and tau biomarkers across 5-year age intervals. c, Overview of the mean and 95% confidence interval ages at which symptoms, MCI and dementia manifest. d, The 95% prediction intervals for various genetically determined forms of AD. Credit: *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02931-w

A team of neurologists affiliated with multiple institutions in Spain and the U.S. has found evidence that suggests up to 20% of all cases of Alzheimer's disease (AD) may be attributable to double copies of the APOE4 gene.

For their paper published in the journal *Nature Medicine*, the group studied data from the brains of thousands of deceased AD patients and biomarkers in an additional 10,000 living patients.

Qin Xu, Zherui Liang and Yadong Huan, with the Gladstone Institute of Neurological Disease, has published a News & Views piece in the same journal issue outlining the work done by the team on this new effort.

AD is a specific type of dementia that involves mental deterioration due to gradual degeneration of the brain. Prior research has found that there are two main kinds of AD; genetic forms and late onset forms. Prior research has also shown that homozygous APOE4 genes (having two copies) is one of the risk factors for the genetic kind of the disease.

In this new study, the research team has found evidence suggesting that AD due to homozygous APOE4 genes should be classified as a third general type of the disease, rather than as a risk factor.

The work by the team involved analyzing pathological data obtained from 3,300 AD patients and data for an additional 10,000 living AD patients collected from multiple medical facilities. They found that 800 of the people included in the study had homozygous APOE4 genes. They also found that virtually all of them had high levels of amyloid levels in their brain fluid by the age of 65—a finding, they suggest, that indicates the disease was fully penetrant in those patients.

They also found that the age at which symptoms became apparent was consistent among those with homozygous APOE4 genes. And,

biomarkers for those with the genes evolved into predictable patterns that were very similar across patients.

Their findings suggest that between 15% and 20% of AD cases may likely be attributable to patients having homozygous APOE4 genes. Taken together, the research team says the evidence indicates that AD cases involving homozygous APOE4 genes should be considered a unique type of AD, and not just a risk factor.

More information: Juan Fortea et al, APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02931-w

Qin Xu et al, APOE4 homozygosity is a new genetic form of Alzheimer's disease, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02923-w