

Untangling APOE ϵ 4's association to tau tangles

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For years, physicians have been aware that patients carrying the apolipoprotein E4 (APOE ϵ 4) gene are at a greater risk of developing Alzheimer's disease. New research from McGill University has now found the gene plays an even greater role in dementia.

In a study published today in the *Journal of the American Medical Association: Neurology*, Dr. Pedro Rosa-Neto's research team from the Douglas Mental Health University Institute's Translational Neuroimaging Laboratory found that the risk of developing dementia conferred by APOE ϵ 4 does in fact involve processes associated to tau aggregation.

A tale of two proteins

Of all the genetics risk factors for sporadic Alzheimer's [disease](#), APOE ϵ 4 is the single most important.

"Alzheimer's disease is defined by the aggregation of two proteins in the brain: [amyloid plaques](#) and tau tangles, both of which are known to be neurotoxic" explains Joseph Therriault, a Ph.D. student in the McGill's Integrated Program in Neuroscience under the supervision of Drs. Pedro Rosa-Neto and Serge Gauthier. "APOE ϵ 4 has been associated with amyloid plaques, but its association with tau tangles has been controversial. In our study of nearly 500 individuals, we demonstrate this association in living humans."

Therriault and his colleagues assessed two independent populations thanks to data available through the Translational Biomarkers in Aging and Dementia (TRIAD) cohort and the Alzheimer's Disease Neuroimaging Initiative (ADNI), two research initiatives in which participating patients agreed to complete a variety of imaging and clinical assessments. In both instances, MRIs and PET scans were used to establish a relationship between APOE ϵ 4 and tau tangles.

Tau tangles and memory

"For years, we have known that people with the APOE ϵ 4 gene have more memory problems," adds Therriault, who is also the study's lead

author. "We were able to show that carriers of this gene also had greater levels of tau tangles in memory centers of the brain, even after controlling for how much amyloid plaques they had."

While this study does not identify a biological mechanism for why this association exists, the findings contribute to an evolving framework in which APOE ϵ 4 plays a central role in Alzheimer's disease because of its role in both amyloid plaques and tau tangles.

Dr. Rosa-Neto adds that APOE ϵ 4 has an important role in the very early stages of Alzheimer's disease. "This paper highlights why APOE ϵ 4 carriers show early memory deficits that eventually lead to dementia," he says.

"Our paper is an important step forward because we provide evidence that the substantial increased risk of developing dementia conferred by APOE ϵ 4 genotype is related to both of the hallmark pathologies of Alzheimer's disease," concludes Therriault.

The team next hopes to determine whether the studied individuals accumulate tau at a faster level through longitudinal imaging to see how subjects evolve over time.

Therriault, Rosa-Neto and Gauthier are hopeful that the research will help clinicians better assess the early signs of Alzheimer's disease.

More information: Joseph Therriault et al. Association of Apolipoprotein E ϵ 4 With Medial Temporal Tau Independent of Amyloid- β , *JAMA Neurol*. Published online December 20, 2019. doi.org/10.1001/jamaneurol.2019.4421

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