APOE E2/E2 genotype offers some protection from cognitive decline

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The APOE gene—coding for a protein involved in lipid transport and implicated in the clearance of amyloid-beta, one of the proteins that builds up in the brain in Alzheimer's disease—exists in three allelic forms: E4, E3, and E2. Researchers have strong evidence that the presence of E4 constitutes a risk factor for Alzheimer's disease.

The role of E2, however, is less clear. A new study led by a Boston University School of Public Health (BUSPH) researcher and published in the *Journal of Alzheimer's Disease*, shows evidence that the E2 gene is associated with a slower rate of cognitive decline with age.

"A lot of attention is paid to genetic traits that put people at higher risk for diseases like Alzheimer's, but understanding genetic traits that seem protective against cognitive decline is also valuable," says study lead author Benjamin Sweigart, a doctoral student in the Department of Biostatistics at BUSPH. "Our results suggest that the E2 allele may play a particularly important biochemical role in slowing cognitive decline. Understanding exactly what it does could help advance the development of therapeutics that slow cognitive decline as we age."

Many previous studies of the E2 allele have focused on middle-aged adults. In other words, they have not explored how the aging process interacts with the allele's protective effects—an important caveat when extrapolating the results to a neurodegenerative disease that progresses with age. Another limitation concerns the rarity of the E2 allele. Because there are relatively few individuals who carry the E2 allele, researchers have needed to group together individuals with two copies of the E2 allele (homozygous individuals) and individuals with only one copy of the E2 allele (heterozygous individuals) when analyzing their data. While necessary for accumulating a large enough sample size to determine statistical significance, the drawback of this approach is that the researchers miss any potential difference in protective effect between individuals with one versus two E2 alleles.

To better understand the role of E2 in mediating cognitive decline, researchers from BUSPH, Boston University School of Medicine, Tufts Medical Center, and Columbia University analyzed genotype data from two large longitudinal cohort studies: the New England Centenarian Study and the Long Life Family Study. The New England Centenarian

Study includes over 4,000 participants comprised of centenarians and their family members. The Long Life Family Study has enrolled about 4,900 participants belonging to long-lived families. Together, these two samples provided the researchers with a sizeable group of individuals carrying the E2 allele.

To determine the effect of E2 allele status on cognitive decline, the researchers used a tool called the Telephone Interview for Cognitive Status (TICS). Every three years in the Long Life Family Study (or, for participants over age 70, every year) and every other year for participants in the New England Centenarian Study, the researchers administered this series of questions designed to screen for cognitive impairment.

After analyzing the genotypes of the participants and comparing their scores on TICS, the researchers found that individuals homozygous for the genotype (E2/E2 individuals) experienced a significantly slower rate of cognitive decline as they got older. None of the other genotypes, however, were significantly different than the E3/E3 genotype. In other words, individuals with only one E2 allele (heterozygous individuals) did not enjoy the same protective effect as did individuals with two E2 alleles (homozygous individuals).

"These findings are consistent with a protective effect of the E2/E2 genotype on episodic memory, working memory, and executive function domains of cognitive function," Sweigart says.

More information: Benjamin Sweigart et al, APOE E2/E2 Is Associated with Slower Rate of Cognitive Decline with Age, *Journal of Alzheimer's Disease* (2021). DOI: 10.3233/JAD-201205