Defying the widely held belief that a specific gene is the biggest risk factor for Alzheimer’s disease, two Cornell developmental psychologists and their colleagues report that people with that gene are more likely to develop mild cognitive impairment – but not Alzheimer’s.

The study suggests that older adults with healthy brain function can get genetic tests to predict increased risk of future mild cognitive impairment. However, once they are impaired cognitively, the tests won’t predict their likelihood of developing Alzheimer’s.

“Right now, genetic tests are used in exactly the opposite way. That is, healthy people don’t get the tests to predict their risk of mild cognitive impairment, but impaired people get them to predict their risk of Alzheimer’s disease,” said Charles Brainerd, professor of human development and the study’s lead co-author with Valerie Reyna, professor of human development. “So, impaired people think that tests will tell them if they are at increased risk of Alzheimer’s, which they won’t. And healthy people think that tests won’t tell them whether they are at increased risk of cognitive impairment, which they will.”

The researchers describe their findings in the January issue of Neuropsychology (27:1).

The work builds on previous research by Brainerd and associates that suggested the ε4 allele of the APOE genotype increases the risk of mild cognitive impairment as well as Alzheimer’s.

The researchers analyzed data from the only nationally representative dataset of its kind, the National Institute on Aging’s Aging, Demographics and Memory Study. They looked at data from 418 people over age 70 to see if those who carried the allele were more likely to develop mild cognitive impairment compared with those who did not have the allele. They also looked at whether ε4 carriers with mild cognitive impairment were more likely to develop Alzheimer’s disease compared with non-carriers with mild cognitive impairment.
They found that healthy ε4 carriers were nearly three times – 58 percent – more likely to develop mild cognitive impairment compared with non-carriers. However, ε4 carriers with mild cognitive impairment developed Alzheimer’s at the same rate as non-carriers.

While previous studies showed that the ε4 allele was more common in people with Alzheimer’s disease, this study shows that it does not increase the risk that healthy or impaired people will become demented. Rather, ε4 increases the risk that healthy people will become cognitively impaired, and impaired people are the primary source of new Alzheimer's diagnoses, Brainerd explained. “The reason ε4 is a risk factor for mild cognitive impairment, but not for progression from mild cognitive impairment to Alzheimer’s disease, is that this allele is a marker of initial cognitive declines – for example, memory and executive function – that are associated with mild cognitive impairment but not of subsequent declines in cognition or in daily functioning that are associated with forms of Alzheimer’s disease.”

Brainerd also noted that the effects of ε4 in healthy adults can be detected by the mid-20s. While ε4 is not a risk factor for the severe cognitive declines that signal dementia, it is risk factor for the weaker declines that eventually produce mild cognitive impairment.

The co-authors of the paper are Ronald Petersen and Glenn Smith of the Mayo Clinic; Anna Kenney ’11, Caroline Gross ’12 and Emily Taub ’10 of Cornell – all of whom helped conduct the research as undergraduates in Brainerd’s lab; Brenda Plassman of Duke University Medical Center; and Gwenith Fisher of the University of Michigan.

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