

Study reveals multiple mechanisms may play role in Alzheimer's

October 2 2012

(Medical Xpress)—Researchers investigating a known gene risk factor for Alzheimer's disease discovered it is associated with lower levels of beta amyloid—a brain protein involved in Alzheimer's—in cognitively healthy older people. The findings suggest that a mechanism other than one related to beta amyloid accumulation may influence disease risk associated with the gene. The study, by researchers at the National Institute on Aging (NIA) at the National Institutes of Health, was published online September 27, 2012 in the journal *Biological Psychiatry*.

The scientists studied a variation in the complement receptor-1 (CR1) gene, a newly identified gene associated with risk for late-onset Alzheimer's disease, in cognitively normal older volunteers. Participants with this gene variant were found to have less brain amyloid than those without the risk variant. In addition, the CR1 [gene variant](#) was found to interact with APOE, the most robust genetic risk factor for Alzheimer's disease, to influence the amount of brain amyloid.

"The prevailing hypothesis has implicated factors increasing [beta amyloid](#) in the brain as an integral element of Alzheimer's [disease pathology](#)," said NIA Director Richard J. Hodes, M.D. " This study indicates the importance of exploring and understanding other distinct mechanisms that may be at work in this disease."

Using a brain scan called Pittsburgh Compound B [positron emission tomography](#) (PiB PET), the researchers measured brain amyloid in 57

cognitively normal older people with an average age of 78.5 in the Baltimore Longitudinal Study of Aging (BLSA). The researchers also looked at PiB PET data from 22 cognitively normal people about the same average age in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Of the 57 BLSA participants, 17 carried the Alzheimer's risk variant of the CR1 gene, while four of the 22 ADNI participants carried the variant.

"We found that brain amyloid burden in the group with the CR1 risk variant was lower than in the group without it. This difference in brain amyloid between the two groups is statistically significant in several brain regions," said lead author Madhav Thambisetty, M.D., Ph.D., chief of the Clinical and Translational Neuroscience Unit in the Laboratory of Behavioral Neuroscience of the NIA's Intramural Research Program. "That suggests to us that the CR1 risk factor gene, if it contributes to Alzheimer's disease, does it in a way unrelated to increasing amyloid burden.

"The findings suggest that the increased risk of Alzheimer's associated with CR1 is not driven by an increase in amyloid in the brain and that we may also need to consider multiple [genetic risk](#) factors in combination," Thambisetty continued. "It may be possible that CR1 acts through other mechanisms, distinct from those that increase amyloid deposition in the brain. These may include influencing inflammation in the brain, but further research is needed to identify what these other mechanisms might be."

The [BLSA](#), established in 1958, is the longest running scientific study of human aging in the United States. BLSA scientists are investigating what happens as people age and how to distinguish changes due to aging from those of disease or other causes. More than 1,400 men and women ranging in age from their 20s to their 90s are study volunteers who come to the NIA laboratories in Baltimore every two years for a battery of

physical and mental exams. More than 3,000 individuals have volunteered since the study began.

[ADNI](#) was launched in 2004 to find imaging methods and fluid biomarkers for Alzheimer's disease that can track and predict clinical change over time. As of fall 2012, ADNI scientists had collected seven years of longitudinal data from more than 1,100 participants at 57 U.S. and Canadian sites. ADNI data, combined with earlier Alzheimer's research, resulted in the general acceptance of the concept that Alzheimer's disease pathology begins several years before any external symptoms appear. ADNI's unprecedented open access data policy is a key component of the study's success.

Provided by National Institutes of Health

Citation: Study reveals multiple mechanisms may play role in Alzheimer's (2012, October 2) retrieved 25 April 2024 from

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