Family history of Alzheimer's associated with abnormal brain pathology

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Close family members of people with Alzheimer's disease are more than twice as likely as those without a family history to develop silent buildup of brain plaques associated with Alzheimer's disease, according to researchers at Duke Medicine.

The study, published online in the journal *PLOS ONE* on April 17, 2013, confirms earlier findings on a known genetic variation that increases one's risk for Alzheimer's, and raises new questions about other genetic factors involved in the disease that have yet to be identified.

An estimated 25 million people worldwide have Alzheimer's disease, and the number is expected to triple by 2050. More than 95 percent of these individuals have late-onset Alzheimer's, which usually occurs after the age of 65. Research has shown that Alzheimer's begins years to decades before it is diagnosed, with changes to the brain measurable through a variety of tests.

Family history is a known risk factor and predictor of late-onset Alzheimer's disease, and studies suggest a two- to four-fold greater risk for Alzheimer's in individuals with a mother, father, brother or sister who develop the disease. These first-degree relatives share roughly 50 percent of their genes with another member of their family. Common genetic variations, including changes to the APOE gene, account for around 50 percent of the heritability of Alzheimer's, but the disease's other genetic roots are still unexplained.

"In this study, we sought to understand whether simply having a positive family history, in otherwise normal or mildly forgetful people, was enough to trigger silent buildup of Alzheimer's plaques and shrinkage of memory centers," said senior author P. Murali Doraiswamy, professor of psychiatry and medicine at Duke.

Duke neuroscience research trainee Erika J. Lampert, Doraiswamy and colleagues analyzed data from 257 adults, ages 55 to 89, both cognitively healthy and with varying levels of impairment. The participants were part of the Alzheimer's Disease Neuroimaging Initiative, a national study working to define the progression of Alzheimer's through biomarkers.

The researchers looked at participants' age, gender and family history of the disease, with a positive family history defined as having a parent or sibling with Alzheimer's. This information was compared with cognitive assessments and other biological tests, including APOE genotyping, MRI scans measuring hippocampal volume, and studies of three different pathologic markers (Aβ42, t-tau, and t-tau/Aβ42 ratio) found in cerebrospinal fluid.

As expected, the researchers found that a variation in the APOE gene associated with a greater risk and earlier onset of Alzheimer's was overrepresented in participants with a family history of the disease. However, other biological differences were also seen in those with a family history, suggesting that unidentified genetic factors may influence the disease's development before the onset of dementia.

Nearly half of all healthy people with a positive family history would have met the criteria for preclinical Alzheimer's disease based on measurements of their cerebrospinal fluid, but only about 20 percent of those without a family history would have met such criteria.

"We already knew that family history increases one's risk for developing

Alzheimer's, but we now are showing that people with a positive family history may also have higher levels of Alzheimer's pathology earlier, which could be a reason why they experience a faster cognitive decline than those without a family history," Lampert said.

The findings may influence the design of future studies developing new diagnostic tests for Alzheimer's, as researchers may choose to exclude those with a positive family history – a group that has historically volunteered to participate in studies to better understand the disease – as healthy controls, given that they are more likely to develop Alzheimer's pathology.

"Our study shows the power of a simple one-minute questionnaire about family history to predict silent brain changes," Doraiswamy said. "In the absence of full understanding of all genetic risks for late-onset Alzheimer's, family history information can serve as a risk stratification tool for prevention research and personalizing care." He encouraged those with a known positive family history to seek out clinical trials specific to preventing the disease.

Provided by Duke University Medical Center