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Study explores genetics behind Alzheimer's resiliency

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Autopsies have revealed that some individuals develop the cellular changes indicative of Alzheimer's disease without ever showing clinical symptoms in their lifetime.

Vanderbilt University Medical Center memory researchers have discovered a potential genetic variant in these asymptomatic individuals that may make brains more resilient against Alzheimer's.

"Most Alzheimer's research is searching for genes that predict the disease, but we're taking a different approach. We're looking for genes that predict who among those with Alzheimer's pathology will actually show clinical symptoms of the disease," said principal investigator Timothy Hohman, Ph.D., a post-doctoral research fellow in the Center for Human Genetics Research and the Vanderbilt Memory and Alzheimer's Center.

The article, "Genetic modification of the relationship between phosphorylated tau and neurodegeneration," was published online recently in the journal *Alzheimer's and Dementia*.

The researchers used a marker of Alzheimer's disease found in cerebrospinal fluid called phosphorylated tau. In brain cells, tau is a protein that stabilizes the highways of cellular transport in neurons. In Alzheimer's disease tau forms "tangles" that disrupt cellular messages.

Analyzing a sample of 700 subjects from the Alzheimer's Disease

Neuroimaging Initiative, Hohman and colleagues looked for genetic variants that modify the relationship between phosphorylated tau and lateral ventricle dilation—a measure of disease progression visible with magnetic resonance imaging (MRI). One genetic mutation (rs4728029) was found to relate to both ventricle dilation and cognition and is a marker of neuroinflammation.

"This gene marker appears to be related to an inflammatory response in the presence of phosphorylated tau," Hohman said.

"It appears that certain individuals with a genetic predisposition toward a 'bad' neuroinflammatory response have neurodegeneration. But those with a genetic predisposition toward no inflammatory response, or a reduced one, are able to endure the pathology without marked neurodegeneration."

Hohman hopes to expand the study to include a larger sample and investigate gene and protein expression using data from a large autopsy study of Alzheimer's disease.

"The work highlights the possible mechanism behind asymptomatic Alzheimer's disease, and with that mechanism we may be able to approach intervention from a new perspective. Future interventions may be able to activate these innate response systems that protect against developing Alzheimer's symptoms," Hohman said.

Provided by Vanderbilt University Medical Center