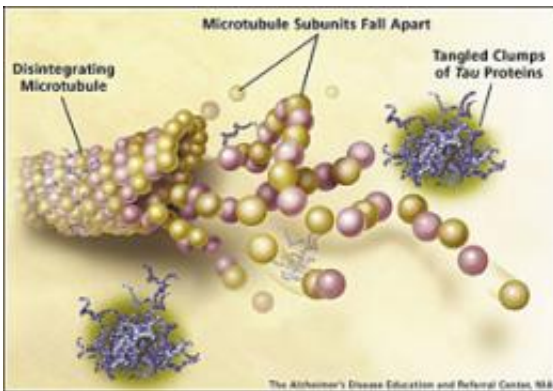


Newly identified genetic marker involved in aggressive Alzheimer's disease

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When neurofibrillary tangles form, brain cells die and release tau. (NATIONAL INSTITUTE ON AGING)

An international team of Alzheimer's disease experts, led by Washington University School of Medicine in St. Louis, has uncovered a gene variation that appears to predict the rate at which Alzheimer's disease will progress.

The investigators report their findings online in the journal *Public Library of Science (PLOS) Genetics*.

Whereas previous studies have focused on factors that influence the risk for Alzheimer's, the new research points to a way to determine how rapidly Alzheimer's patients may develop full-blown dementia after their

diagnosis.

The investigators studied 846 patients with elevated levels of a protein called tau in their cerebrospinal fluid (CSF). Recent studies have found that the presence of a particular form of the tau protein in the CSF is an indicator of Alzheimer's disease. The researchers also looked at single DNA variations in the patients and identified a genetic marker linked to elevated tau levels. That marker turned out to be associated with rapid progression of Alzheimer's disease.

"People who carry this genetic marker tend to have higher tau levels at any given stage of the disease than individuals without it," says senior investigator Alison M. Goate, DPhil., the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry. "Until now, most studies of genetic risks associated with Alzheimer's disease have looked at the risk of developing the disease, not the speed at which you will progress once you have it. The genetic marker we've identified deals with progression."

For many patients and their families, that information may be more useful than the knowledge that a person may be developing Alzheimer's damage in the brain even if that individual hasn't yet developed clinical symptoms, according to Goate. Damage from the disease can be present for years before symptoms appear. But this study suggests that elevated tau, combined with the genetic marker, could be a sign that clinical symptoms may quickly advance from mild impairment to severe dementia.

The study advances recent research that found it was possible to diagnose Alzheimer's disease, even in patients with no clinical symptoms, by measuring levels of the amyloid beta protein in the CSF. A-beta makes up the senile plaques that form in the brains of Alzheimer's patients, but it turns out that low levels of A-beta in the CSF predict the presence of Alzheimer's pathology in the brain.

Meanwhile, the tau protein collects in the other abnormal brain structures that characterize the illness, called neurofibrillary tangles. The tangles cause brain cells to die, and when those cells die, tau is released into the CSF. So just as low A-beta levels in the CSF are associated with Alzheimer's disease, elevated tau levels also indicate the presence of disease.

"Tau also can be released in stroke patients or those with other types of brain injuries," says first author Carlos Cruchaga, PhD. "However, a particular form of tau is specific to Alzheimer's. It's a phosphorylated form of the protein called ptau. Other neurodegenerative conditions, like Parkinson's disease, don't produce elevated ptau in the CSF. It's only found in Alzheimer's disease."

Cruchaga, an assistant professor of psychiatry at Washington University, says there was no association between ptau and overall Alzheimer's disease risk or age of onset for Alzheimer's patients, but there was a significant association between a variant of a gene that plays a role in modifying the tau protein, ptau levels in the CSF and the rate at which the disease progressed.

"We have looked at data from three separate, international studies, and in all three, we found the same association," Cruchaga says. "So we are confident that it is real and that this gene variant is associated with progression in Alzheimer's disease."

He says the genetic finding, combined with the ability to measure ptau in the CSF may mean that if drugs could inhibit the protein's accumulation in the fluid, it might prevent or delay some of the devastation associated with Alzheimer's disease.

"If we could somehow decrease tau pathology in those individuals who also have low levels of A-beta in the CSF, we might be able to slow the

progression of the disease," Cruchaga says.

Goate says the findings might initially be most useful in the design of clinical trials. If researchers knew in advance that particular study patients were going to progress at a rapid rate, they could better evaluate the effects of drugs designed to slow the progression of Alzheimer's disease.

"I think that if the drug target is A-beta, then treatment really needs to begin even before someone develops symptoms," Goate says. "In contrast, since most of the changes in tau occur after someone already has symptoms, it may be possible to target that pathway to slow progression of the disease, by interfering with the actions of the tau protein."

More information: Cruchaga C, Kauwe JSK, Mayo K, Spiegel N, Bertelsen S, et al. (2010) SNPs Associated with Cerebrospinal Fluid Phospho-Tau Levels Influence Rate of Decline in Alzheimer's Disease. PLoS Genet 6(9): e1001101. [doi:10.1371/journal.pgen.1001101](https://doi.org/10.1371/journal.pgen.1001101)

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