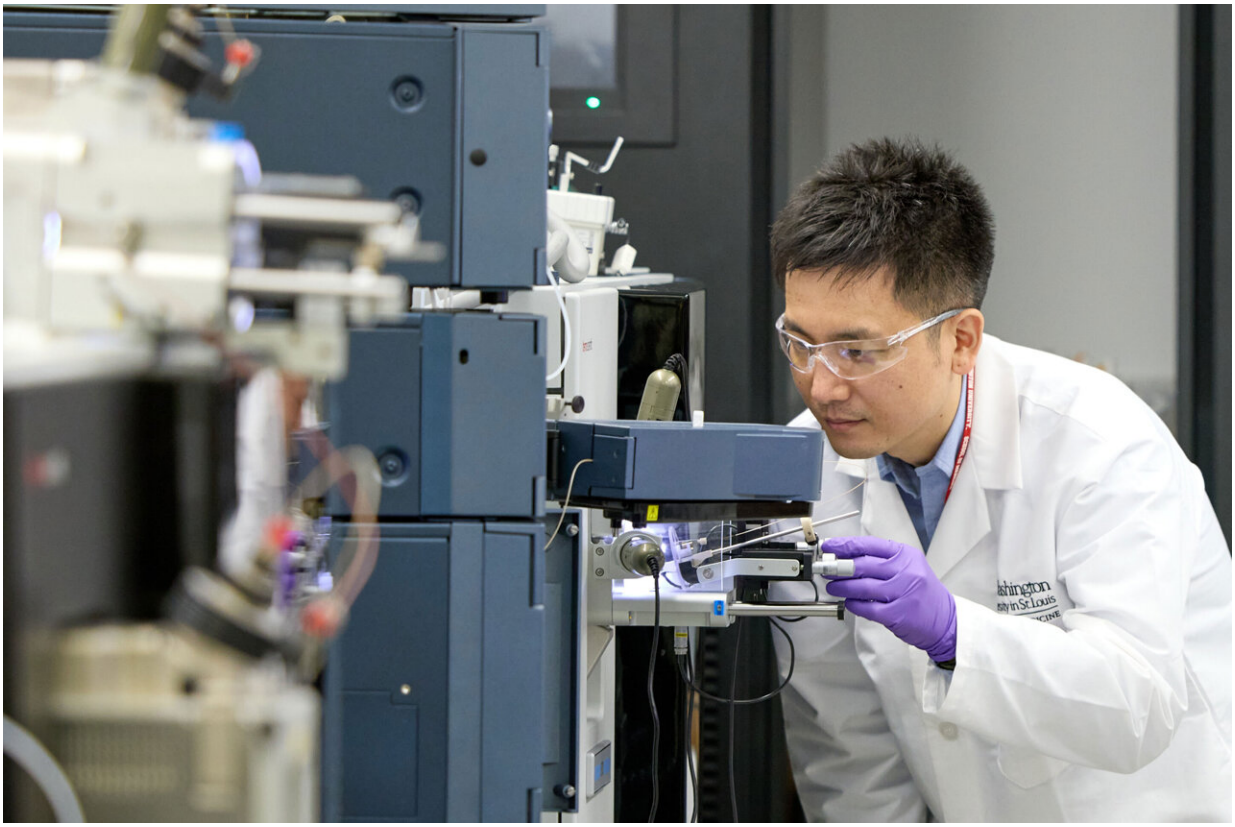
Tau-based biomarker tracks Alzheimer's progression

July 13 2023



Kanta Horie, PhD, works with a mass spectrometer that he uses to measure protein levels in cerebrospinal fluid samples. Horie and colleagues at Washington University School of Medicine in St. Louis and Lund University in Sweden have discovered that a form of the protein tau in the cerebrospinal fluid known as MTBR-tau243 can be used to track the progression of Alzheimer's disease and could speed drug development. Credit: Matt Miller/Washington University

Two pathologies drive the progression of Alzheimer's disease. Early on, amyloid beta plaques lead the way, but around the time cognitive symptoms arise, tau tangles take over as the driving force and cognition steadily declines. Tracking the course of the disease in individual patients has been challenging because there's been no easy way to measure tau tangles in the brain.

But now, researchers at Washington University School of Medicine in St. Louis and Lund University in Lund, Sweden, have identified a form of tau that could serve as a marker to track Alzheimer's progression.

The marker also could be used by Alzheimer's drug developers to assess whether investigational tau-based drugs—the next frontier in Alzheimer's drug development—are effective against the disease. Such drugs theoretically would benefit people in later stages of the disease, when tau tangles play a crucial role.

By studying 667 people in Sweden and the U.S. at various stages of Alzheimer's disease, the researchers discovered in the cerebrospinal fluid that levels of a specific form of tau—known as microtubule binding region (MTBR)-tau243—track with the amount of damaging tau tangles in the brain and with the degree of cognitive decline.

The findings, published July 13 in *Nature Medicine*, are a major step toward a better approach to diagnosing and staging Alzheimer's disease. A test based on MTBR-tau243 could speed up drug development by providing a relatively simple and inexpensive way to identify and monitor participants in clinical trials and assess whether the experimental therapies, including tau-based drugs, can change the course of the disease.

"This discovery provides biomarkers to specifically track the progression of tau tangles, the major pathology that predicts dementia and cognition,

which is something that hasn't been within reach until now," said co-senior author Randall J. Bateman, MD, the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University.

"These findings will help accelerate drug development for patients with symptoms of Alzheimer's disease. We are also working on developing these biomarkers as a clinical test to stage individual patients and improve patient care."

The gold standard for measuring tau tangles in the brain is the tau-positron emission tomography (tau-PET) brain scan, which costs thousands of dollars and requires expensive equipment and specialized expertise not available at most hospitals, making such scans impractical for patient care and costly for research studies.

In 2020, Bateman and Kanta Horie, Ph.D., a research associate professor of neurology and co-first author on the new paper, showed that levels of MTBR-tau243 in the cerebrospinal fluid reflect the amount of tau tangles in the brain. In this new study, Bateman and Horie teamed up with Lund University's Oskar Hansson, MD, Ph.D., a professor of neurology and study co-senior author, and Gemma Salvadó, Ph.D., a postdoctoral researcher and co-first author, to extend the analysis to a larger number of people and to compare MTBR-tau243 to other tau biomarkers.

The researchers analyzed data from people who volunteered for Alzheimer's research studies through the Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER)-2 (448 people) study in southern Sweden or the Knight Alzheimer Disease Research Center (219 people) in St. Louis.

The average age of participants was 71, and the group included healthy people as well as people at all stages of disease, ranging from those with

some amyloid in their brains but no cognitive symptoms, to those with extensive amyloid and tau in their brains and a diagnosis of dementia. The researchers compared cognitive function with levels of various forms of tau in the cerebrospinal fluid and with levels of amyloid and tau in the brain, as measured by amyloid and tau PET scans.

Levels of MTBR-tau243 in the cerebrospinal fluid correlated strongly with brain tau tangle levels and cognitive function. As MTBR-tau243 levels went up, tau levels in the brain also went up, and scores on cognitive tests went down. In contrast, levels of another form of tau in the cerebrospinal fluid, phosphorylated tau, tracked mainly with brain amyloid levels but not with brain tau levels or cognitive function.

"To accurately diagnose Alzheimer's disease in patients with cognitive symptoms, we need biomarker-based evidence of both amyloid beta plaques and tau tangle pathology," Hansson said. "With this new biomarker, representing tau pathology, we can do this using a single cerebrospinal fluid sample. This has the potential to clearly improve the diagnostic as well as prognostic work-up of Alzheimer's worldwide. We hope that we soon can do the same using a simple blood test."

By combining the two forms of tau in the cerebrospinal fluid—phosphorylated tau and MTBR-tau243—the researchers were able to predict cognitive function almost as well as by using tau-PET.

"A combination of phosphorylated tau and MTBR-tau243 in the cerebrospinal fluid reveals not only whether an individual has Alzheimer's disease but identifies the stage of illness—from presymptomatic disease to full-blown dementia," Horie said.

By taking repeated samples of cerebrospinal fluid, researchers could track the progression of the disease and determine the effect of interventions such as experimental anti-tau therapeutics on the disease

trajectory.

"In late stages of Alzheimer's disease, the effectiveness of anti-amyloid therapies may weaken because amyloid is no longer playing a major role in driving the disease," Horie said. "But that's when tau becomes relevant. By stopping the tau pathology, we may be able to stop further cognitive decline including memory loss. By maintaining individuals at the level of mild cognitive impairment and preventing further cognitive decline, we can help people maintain a good quality of life. That's what we're working toward."

More information: Oskar Hansson, CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02443-z. www.nature.com/articles/s41591-023-02443-z

Provided by Washington University School of Medicine