Genes overseeing tau function identified for the first time

A gene encoding a protein associated with tau production: TRIM11, has been found to inhibit progression while improving cognition and motor performance in small animal models of Alzheimer's disease (AD)-like neurodegenerative diseases, according to new research from the Perelman School of Medicine at the University of Pennsylvania. Furthermore, TRIM11 was identified as playing a key role in the removal of protein tangles that lead to neurodegenerative diseases such as AD. The findings were published in the journal *Science*.

Alzheimer's disease is the most common cause of dementia in older adults, a progressive brain disorder that slowly destroys memory and thinking skills. Basic research at the Penn School of Medicine is led by Dr. Virginia M.Y. Lee (John H. Ware III Professor of Alzheimer's Disease Pathology and Laboratory Medicine Research) and the late John Q. Trojanowski, Ph.D. (Geriatrics and Pathology and Laboratory Medicine Professor of Gerontology in the Laboratory of Medicine), revealed that one of the underlying causes of neurodegenerative disease is neurofibrillary tangles (NFTs) of the [tau protein](https://www.creativebiomart.net/symbolsearch_tau.htm), which cause neuronal death and trigger symptoms of ADHD, such as memory loss.

In addition to AD, aggregation of tau protein into NFTs has been linked to more than 20 other dementias and movement disorders, including progressive supranuclear palsy, Pick's disease, and chronic traumatic encephalopathy, collectively known as tauopathies. However, in patients with these diseases, how and why tau protein clumped together and formed the fibrillar aggregates that make up NFTs remained unclear. This major knowledge gap poses challenges for researchers to develop effective treatments.

"Most organisms have protein quality control systems that remove defective proteins and prevent the accumulation of misfolding and tangles, like the tau protein we see in the brains of tauopathies," said Xiaolu Yang, Ph.D., professor of cancer biology at the University of Pennsylvania. But until now, we didn't know how this works in humans, or why it works in some individuals and not in others. For the first time, we have identified a gene that oversees tau function and has a promising target for developing treatments to prevent and slow the progression of Alzheimer's disease and other related diseases.”

Yang and his team, including first author Zi-Yang Zhang, Ph.D., previously discovered that the TRIM protein plays an important role in protein quality control in animal cells. After examining more than 70 human TRIMs, they found that [TRIM11](https://www.creativebiomart.net/symbolsearch_trim11.htm) plays an important role in inhibiting tau aggregation. TRIM11 has three main functions related to tau protein quality control. First, it binds to tau proteins, especially mutant variants that cause disease, and helps eliminate them. Second, it acts as a "chaperone" for tau, preventing the protein from misfolding. Finally, TRIM11 dissolves pre-existing tau aggregates.

Using postmortem brain tissue from 23 Alzheimer's patients and 14 healthy controls from the Center for Neurodegenerative Disease Research's Tissue Bank, the researchers found TRIM11 protein levels were significantly lower in the brains of Alzheimer's patients compared with healthy controls.

To determine the potential utility of TRIM11 as a therapeutic drug, the researchers used an adeno-associated viral vector (AAV), a tool commonly used in gene therapy, to deliver the TRIM11 gene into the brains of several mouse models. The researchers found that tau-lesioned mice that received the TRIM11 gene had significantly reduced development and accumulation of NFT and greatly improved cognitive and motor performance.

"Not only do these findings tell us that TRIM11 could play an important role in protecting people from Alzheimer's and similar diseases, but we also see that we may be able to develop future treatments that work at lower levels of TRIM11 supplementation in individuals. Together with our colleagues, we are eager to explore the possibility of developing gene therapies to halt the progression of neurodegenerative diseases."