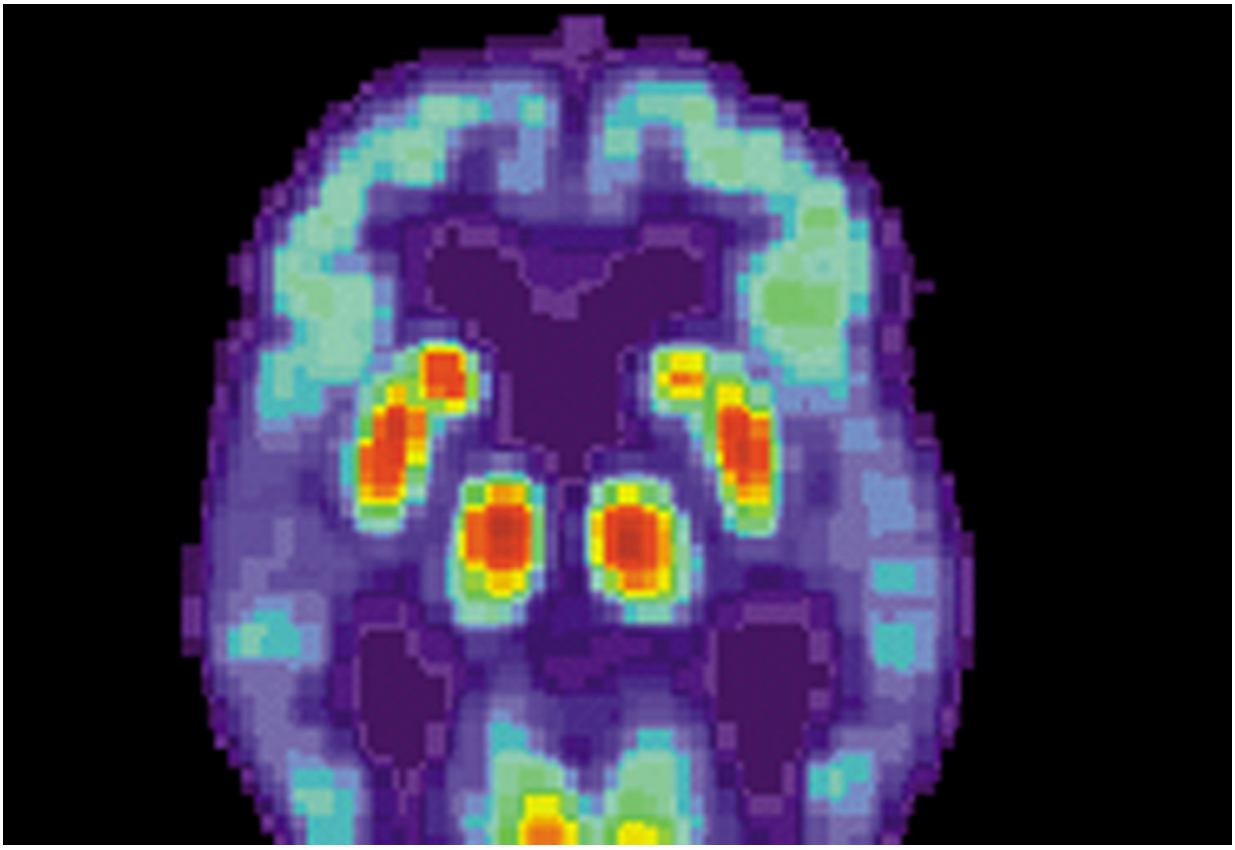
Unusual mechanism in rare mutation associated with Alzheimer's uncovered

April 2 2021



PET scan of a human brain with Alzheimer's disease. Credit: public domain

A novel mechanism has been identified that might explain why a rare mutation is associated with familial Alzheimer's disease in a new study by investigators at the University of Chicago. The paper, published on

April 2 in the *Journal of Experimental Medicine*, characterizes a mutation located in a genetic region that was not previously thought be pathogenic, upending assumptions about what kinds of mutations can be associated with Alzheimer's Disease.

Alzheimer's, a neurodegenerative disease that currently affects more than 6 million Americans, has been characterized by the accumulation of Aβ peptides into plaques in the spaces between neurons in the brain. These Aβ peptides are generated when a larger precursor protein, APP, is cleaved into smaller fragments as APP transits through different cellular compartments.

Most mutations that have previously been associated with Alzheimer's lie either within or just next to a region of the APP gene that codes for the eventual Aβ peptide fragment. However, while the mutation studied by the research team is located in the APP gene, itis quite far from the area where previously characterized mutations are found. The mutation, S198P, was first found in two patients affected by Alzheimer's, and raised eyebrows due to its distance from known disease-associate mutations.

"This mutation, which is not in the region of APP that codes for the Aβ fragment, was so interesting because it was so far away from where all the other mutations are normally located," said senior author Sangram Sisodia, Ph.D., the Thomas Reynolds Sr. Family Professor of Neurosciences at UChicago, "Thus it was not clear how this mutation might be contributing to the pathology of the disease."

The investigators, led by Xulun Zhang, Ph.D., a Research Professional in the Sisodia lab, examined how S198P could affect Aβ peptide production by studying both cultured cells and mice. They found that the presence of the S198P mutation resulted in both cultured cells and mice having elevated levels of Aβ peptides. To further understand why S198P

caused elevated Aβ levels, the authors looked at different steps of the APP-to-Aβ production pipeline.

Using cultured cells, the authors found that S198P causes APP to fold more quickly, allowing Aβ peptides to be produced from mature APP more quickly than from APP that did not contain the S198P mutation. "The rapid folding enhances the egress of APP through the cellular compartments where Aβ is made, allowing faster production of the Aβ peptide" said Sisodia. Mice harboring S198P also had more plaques causes by Aβ accumulation, reinforcing the likelihood that the mutation does indeed contribute to disease.

However, like with many other mutations, the presence of S198P is not a guarantee that Alzheimer's will develop. "This variant is only partially penetrant," said Sisodia, meaning that not every person with S198P will go on to develop Alzheimer's. Similar to mutations in the breast cancer genes BRCA1/2, S198P influences only the probability that an affected person will develop Alzheimer's.

"Geneticists would argue that this is not a pathogenic mutation because you can find this mutation in unaffected people, but this is a complex disease and studying these rare variants uncovers new biology," said Sisodia.

The fact that S198P is located so far away from previously characterized mutations underscores that there is much to still be understood about Alzheimer's. "A lot of mutations that have been described for the past 20 years have been dismissed because they don't look like they follow the normal rules. We need to pay attention to these rare variants because they open up new areas of investigation to completely decipher this disease," said Sisodia.

Though effective treatments for Alzheimer's still remain in

development, Sisodia believes his group's findings argue for a renewed focus on Aβ peptides. "Failures in clinical trials have led some people to think that maybe Aβ has nothing to do with this disease, but these results clearly support a role for Aβ in disease pathogenesis. I hope this revives people's notions about the importance of Aβ in Alzheimer's."

The identification of S198P's mechanism has led Sisodia to plan to go back to other overlooked mutations and investigate them as well. "There are all these other rare variants that were seemingly benign according to other people, but we know from clinical studies that they too drive Alzheimer's pathology and clinical phenotypes," said Sisodia. "We figured out S198P, great! Now let's move on to all these other variants!"

More information: Xulun Zhang et al, An APP ectodomain mutation outside of the Aβ domain promotes Aβ production in vitro and deposition in vivo, *Journal of Experimental Medicine* (2021). DOI: 10.1084/jem.20210313

Provided by University of Chicago Medical Center