Study reveals mechanism behind most common form of inherited Alzheimer's disease

March 4 2015

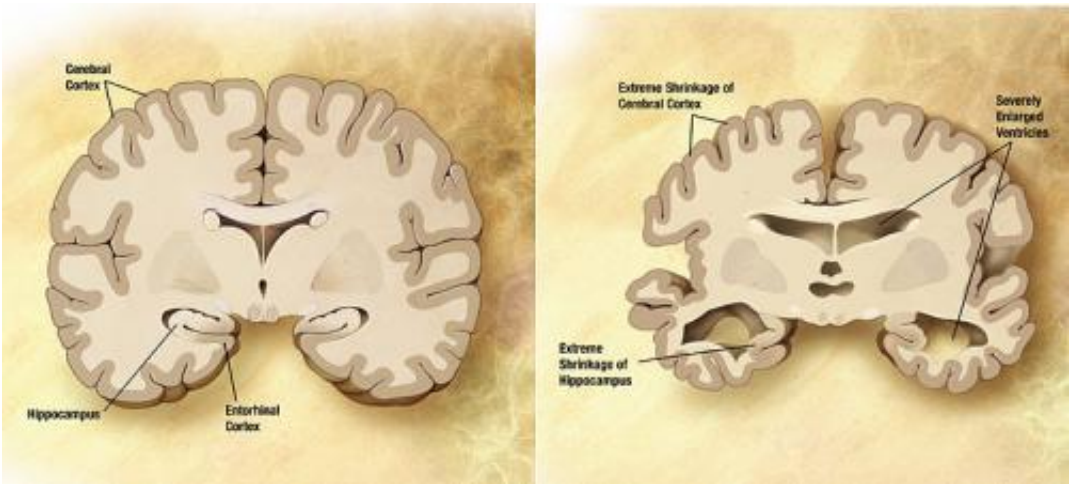


Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

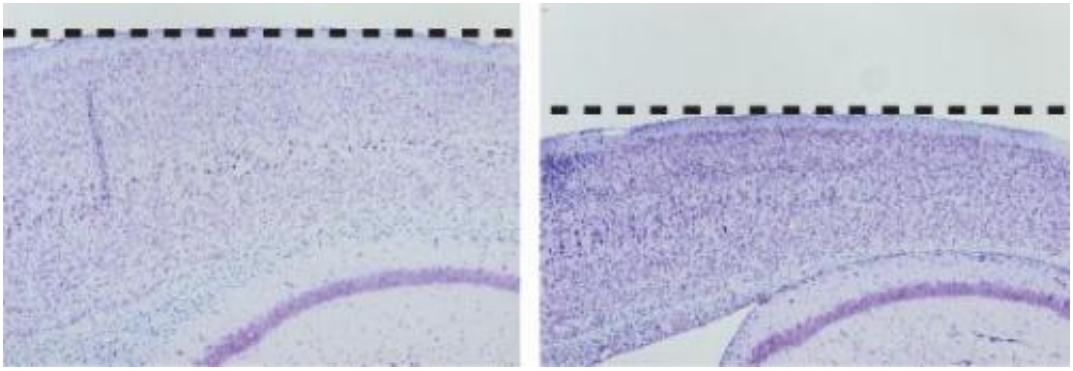
A study from researchers at Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) reveals for the first time exactly how mutations associated with the most common form of inherited Alzheimer's disease produce the disorder's devastating effects. Appearing in the March 4 issue of *Neuron*, the paper upends conventional thinking about the effects of Alzheimer's-associated mutations in the presenilin genes and provides an explanation for the failure of drugs designed to block presenilin activity.

"Our study provides new insights into Alzheimer's disease by showing how human mutations that cause the disease lead to neurodegeneration and dementia," says Raymond J. Kelleher III, MD, PhD, of the MGH Department of Neurology and Center for Human Genetic Research, co-senior author of the *Neuron* paper. "We found that mutations in the presenilin-1 gene promote the hallmark features of the disease by decreasing, rather than increasing, function of the presenilin-1 protein and the gamma-secretase enzyme. In addition to the important therapeutic implications of our findings, we have also generated the first animal model in which an Alzheimer's-disease-causing mutation produces neurodegeneration in the cerebral cortex."

While inherited or familial Alzheimer's disease (FAD) is very rare, accounting for only around 1 percent of cases, the identification more than 20 years ago of the genes that cause FAD provided the first clues into the mechanism behind the effects of the disease. The rarest FAD-associated mutations are found in the amyloid precursor protein (APP), which is clipped by multiple proteases to produce the beta-amyloid peptides that accumulate into the amyloid plaques characteristic of the disease. Mutations in two presenilin genes - which encode essential components of gamma secretase, one of the proteases that process APP - account for around 90 percent of FAD cases. Individuals with presenilin-associated FAD develop Alzheimer's symptoms even earlier than do those with APP mutations.

While the mechanism by which presenilin mutations cause neurodegeneration has not been known, the general thinking was that they increase presenilin and gamma secretase activity, resulting in overproduction of beta-amyloid and particularly of beta-amyloid 42, which is thought to be more prone to deposition in plaques. As a result, development of gamma secretase inhibitors has been a major therapeutic effort pursued by pharmaceutical companies. But Jie Shen, PhD, of the Ann Romney Center for Neurologic Diseases at BWH, co-senior author

of the *Neuron* paper, questioned this widely held view and the use of gamma secretase inhibitors to treat of Alzheimer's disease because her earlier investigations into the normal function of the presenilin genes showed that genetically suppressing presenilin and gamma secretase activity in adult mice caused Alzheimer's-like neurodegeneration, results that contrasted with those of studies in which the overproduction of beta-amyloid or presenilins failed to produce neurodegeneration.



This image compares sections of cortex from a control mouse (left) to a mouse with a presenilin-1 mutation (right). The dashed line indicates the surface of the brain. Presenilin-1 mutations decrease gamma-secretase activity and cause features of neurodegeneration, including shrinkage of the cortex, as shown above. Credit: Raymond Kelleher and Jie Shen, Harvard Medical School.

In a 2007 paper published in *PNAS*, Shen and Kelleher - who had been treating FAD patients with mutations in the presenilin-1 gene and researching brain mechanisms underlying cognitive function - proposed what they termed the presenilin hypothesis: that a loss of presenilin function may be the primary event triggering neurodegeneration and dementia in FAD. In recent studies, Kelleher identified a novel FAD-causing presenilin-1 mutation that inactivated its function in a sensitive cell culture system. In collaboration with Shen, his group went on to

show that a series of FAD mutations all impaired presenilin-1 function in cell culture.

These findings raised the pivotal question of how such mutations affected presenilin-1 function in living animals, especially in the brain. While Shen's earlier investigations had used strains of mice in which one or more copies of the presenilin genes were totally inactivated, for this study she and Kelleher generated mice in which specific, FAD-associated presenilin-1 mutations were "knocked in" to the gene, causing them to be expressed just as they are in human patients with that particular mutation. One of the mutations they tested is relatively common among FAD patients, while the other is fairly rare; and both are located near the site where the protein interacts with its target molecules, when incorporated into gamma secretase.

As was the case with animals in which both copies of presenilin-1 were deleted in earlier studies, those in which both copies were mutated did not survive after birth. Mice in which a single presenilin-1 gene was mutated survived, but showed deficiencies in learning and memory compared with control mice. Production of beta-amyloid within the brains of these mice was actually reduced, although the ratio between forms of the peptide was changed, with proportionally more plaque-associated beta-amyloid 42 being generated. Closer examination of the brains of mice with the FAD mutation showed the same sort of synaptic dysfunction and age-associated neurodegeneration seen in the brains of patients with Alzheimer's disease.

"This paper clearly shows that these FAD mutations cause a loss of presenilin function and gamma secretase activity, leading to the loss of neurons in the adult brain," says Shen. "The most important implication of our findings is that strategies that enhance rather than inhibit gamma secretase should be investigated as potential Alzheimer's therapies. They also may explain why a major clinical trial of a gamma secretase

inhibitor failed to help patients and actually worsened their cognitive abilities." She adds that their presenilin hypothesis does not rule out a role for beta-amyloid in Alzheimer's pathology, it just places presenilin/gamma secretase activity closer to the pathway that leads to neurodegeneration.

While this study only examined presenilin-1 mutations, Kelleher notes, the researchers believe that loss of function is a general property of FAD mutations in both presenilin genes. Investigation of the mechanisms underlying the effects of the APP mutations is also warranted, as is examination of how presenilin dysfunction may contribute to the common, late-onset form of Alzheimer's disease. "Shared or convergent molecular pathways may be responsible for pathogenesis in both familial and sporadic forms, and we hope that mechanistic relationships will become clearer with the identification of genetic risk factors for sporadic or late-onset Alzheimer's disease," he says. "We're now actively pursuing strategies to develop candidate therapies that restore presenilin-1 function. We also hope that our knockin mouse model will facilitate development and preclinical testing of these and other agents that can combat neurodegeneration in Alzheimer's disease."

Provided by Massachusetts General Hospital