Alzheimer's genetics point to new research direction

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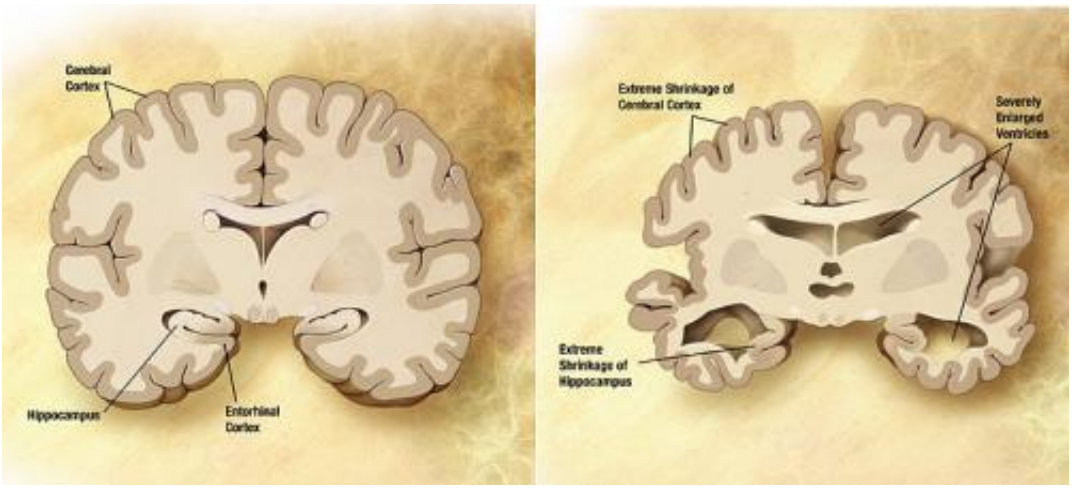

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

A University of Adelaide analysis of genetic mutations which cause early-onset Alzheimer's disease suggests a new focus for research into the causes of the disease.

Previous research has revolved around the idea that accumulation in the brain of a small, sticky protein fragment — amyloid beta — causes Alzheimer's disease.

However, there is growing concern among researchers that this idea is not rapidly advancing global understanding of the disease or leading to

successful treatments.

The University of Adelaide scientists, in collaboration with researchers from a number of other Australian universities, say their analysis points to a new theory about how mutations of a particular gene, PSEN1, can trigger early onset Alzheimer's disease.

"Most of the mutations that cause Alzheimer's disease before retirement age are found in the PSEN1 gene," says study leader, Associate Professor Michael Lardelli, School of Biological Sciences. "Fortunately, this early onset form of Alzheimer's disease accounts for only about 1% of all disease cases. Nevertheless, a huge research effort has focused on these mutations in the hope that advanced genetics analysis techniques might shed light on the still mysterious origins of both early and late onset Alzheimer's disease."

Published in the *Journal of Alzheimer's Disease*, the researchers examined past research on PSEN1 and noted a particular correlation between the types of mutations affecting this gene and whether or not they caused Alzheimer's disease.

"The protein normally produced by the PSEN1 gene is remarkable since it plays so many different roles in cells," says Associate Professor Lardelli. "Almost everyone has been looking at how mutated PSEN1 protein affects production of amyloid beta. However, we think a broader, more holistic view of the mutation data not focused on amyloid beta may be telling a different story."

"There are two pathways that PSEN1 protein can take when it functions in cells. One pathway leads to production of amyloid beta while the second, less-studied pathway controls many other important activities including how cells recycle their components and respond to restricted oxygen availability.

"We suggest that changes in this second pathway are better correlated with how mutations affect the structure of PSEN1 protein and the other proteins it interacts with. By taking our focus away from amyloid beta the mutation data seem to make more sense."

"An exciting possibility is that the fundamentals of our idea may be extended to understanding the much more common late onset form of Alzheimer's disease. That is something we are currently investigating with our animal models of the disease," says Associate Professor Lardelli.

More information: Tanya Jayne et al. Evidence For and Against a Pathogenic Role of Reduced γ-Secretase Activity in Familial Alzheimer's Disease, *Journal of Alzheimer's Disease* (2016). DOI: 10.3233/JAD-151186

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