Root cause of Alzheimer's may be fat buildup in brain cells, research suggests

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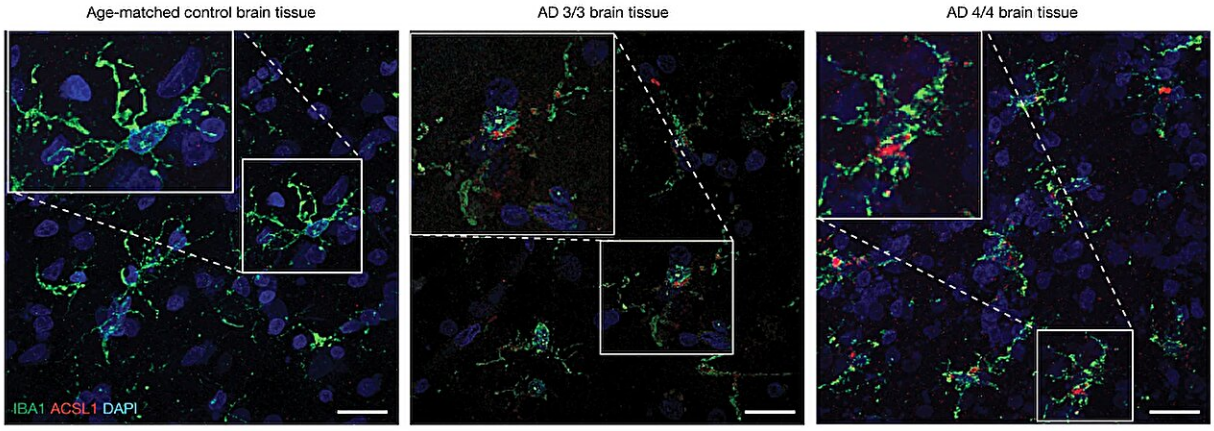

Representative immunofluorescence images of human frontal cortex adjacent to the tissue used in snRNA-seq experiments stained for microglia marker IBA1 (green), ACSL1 (red) and DAPI (blue) in an aged-matched healthy control subject (left), an AD-APOE3/3 subject (middle) and an AD-APOE4/4 subject. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07185-7

A team of neurologists, stem cell specialists and molecular biologists affiliated with several institutions in the U.S. and led by a group at Stanford University School of Medicine has found evidence that the root cause of Alzheimer's disease may be fat buildup in brain cells. The study

is published in the journal *Nature*.

Prior research has suggested that Alzheimer's disease is caused by a buildup of beta-amyloid in plaques that grow between nerve cells. Other work has also implicated a protein called tau, which can build up in brain cells. Thus, most work involved in developing ways to prevent, slow or stop the disease is based on reducing or eliminating such buildups. But as the researchers with this new effort have found, there may be something else at the root of the development of the disease.

Back when Alzheimer's disease was first identified by Alois Alzheimer, he noted that in addition to the plaques and tau buildup, there was also a buildup of fat droplets in brain cells. Since that time, little effort has been made to determine whether they might be the cause of the disease.

The research team therefore focused on the function of the APOE gene—prior research has shown that it encodes for a protein involved in transporting fat droplets into nerve cells. Prior research has also shown that there are four APOE variants, numbered 1 through 4, and that one of them, APOE4, carries the most fat into brain cells, while APOE2 brings the least.

The team wondered if the APOE variants carried different risks for developing Alzheimer's disease. To find out, they conducted a few experiments.

In the first experiment, the researchers used single cell RNA sequencing to identify the proteins inside of a test nerve cell. They applied what they found to tissue samples collected from people who died of Alzheimer's disease who had dual copies of APOE4 or APOE3.

They found that the brains of people with the APOE4 gene had more immune cells with a type of enzyme that boosted movement of fat droplets into brain cells. In another experiment, they found that applying amyloid to brain cells of people with the APOE4 or APOE3 variants made the cells accumulate more fat.

According to the researchers, the results indicate that buildup of amyloid in the brain triggers the push of fat into brain cells, leading to Alzheimer's disease.

More information: Michael S. Haney et al, APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia, *Nature* (2024). DOI: 10.1038/s41586-024-07185-7