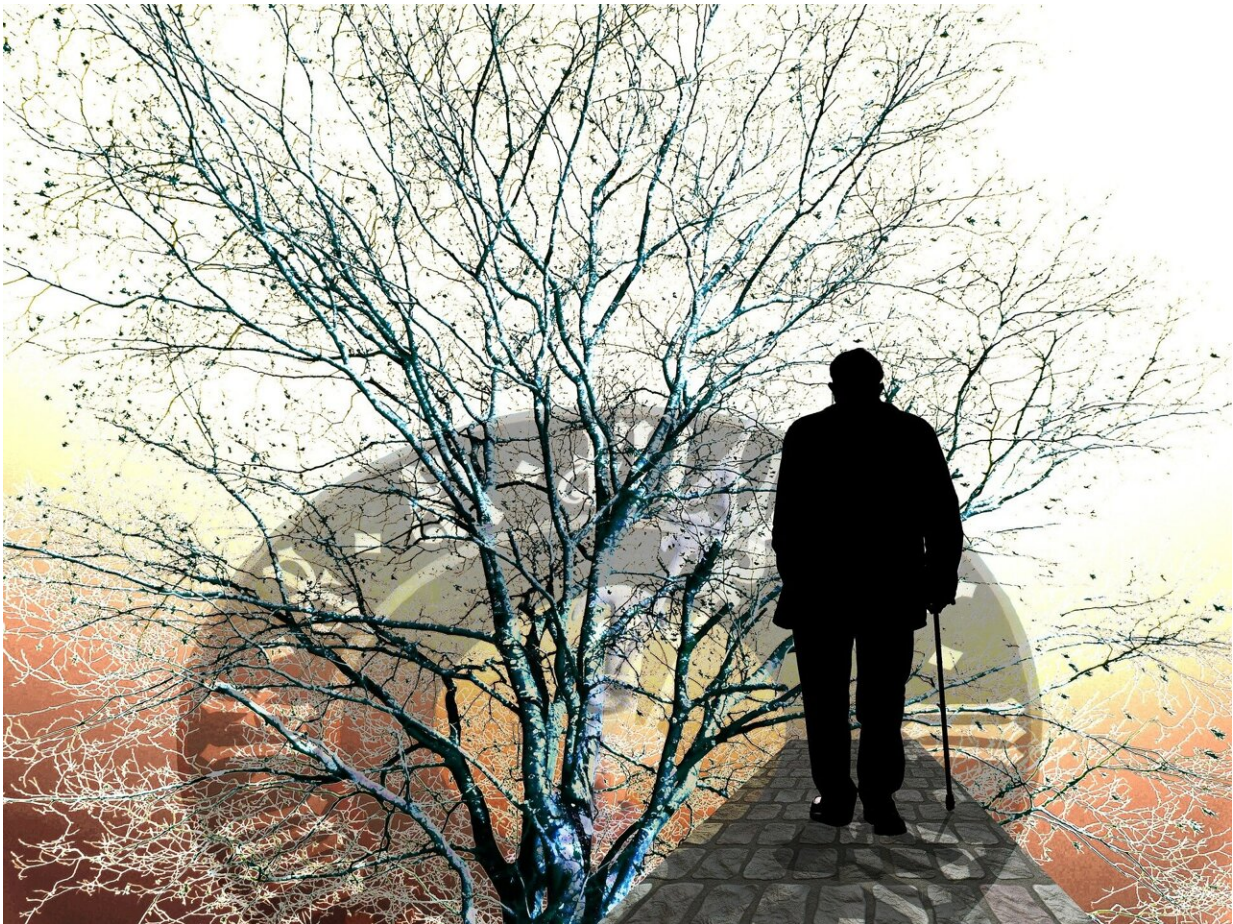


Stem cell research sheds light on new 'molecular road' to Alzheimer's disease

August 22 2023



Credit: Pixabay/CC0 Public Domain

Alzheimer's disease (AD) varies widely in its age of onset, presentation

and severity. Recently, the SORL1 gene has received increased attention since variations in this gene have been associated with both early and late onset AD. However, little is known about how damage to SORL1 leads to disease.

Using stem cells from patients with AD, investigators from Brigham and Women's Hospital, a founding member of the Mass General Brigham health care system, found that loss of normal SORL1 function leads to a reduction in two key proteins known to be involved in AD and which play an essential role in the neurons of healthy individuals. Their results, published in *Cell Reports*, suggest a potential new strategy for AD treatment, especially for patients not responsive to existing therapies.

"Understanding the subtypes of AD is relatively new in the field of neurology research," said corresponding author Tracy Young-Pearse, Ph.D., of the Ann Romney Center for Neurological Diseases. "This is getting at a precision neurology approach, with which we can better predict which patients may be responsive to Alzheimer's treatment strategies that attack [specific genes](#) or target the problems they cause."

Historically, researchers have studied three potent genetic drivers of AD (APP, PSEN1 and PSEN2), which are commonly mutated in hereditary, early-onset AD (AD diagnosis before age 65).

Preclinical models and cell-based systems largely rely on mutations in these genes to model AD, even though in many people with late-onset ("sporadic") AD, a more complex interaction between genes, lifestyle, and environment determines the presentation of AD. Key neurological features of AD, including the abundance of amyloid-beta plaques in the brain, also vary across individuals.

Brigham researchers played a [leadership role](#) in understanding the molecular and [genetic basis](#) for AD, including making key discoveries

related to the amyloid protein. Two novel anti-amyloid therapies, aducanumab and lecanemab, have received United States Food and Drug Administration accelerated and traditional approval, respectively, but not all patients respond to these drugs, warranting other treatment options.

In this new study, the researchers utilized a stem-cell based approach that examined natural genetic variability in AD patients to gain insight into an alternative pathway driving disease. The researchers used CRISPR technologies to remove the SORL1 gene from progenitor stem cells, derived from participants in two Alzheimer's research cohorts, the Religious Order Studies and Rush Memory and Aging Project. They programmed the [stem cells](#) to differentiate into four different kinds of brain cells to examine the impact of removing SORL1 on each cell type.

The most dramatic impact was seen in neurons and a "support" cell in the brain (astrocytes), with neurons lacking SORL1 demonstrating especially prominent reduction in the levels of two key AD proteins: APOE and CLU. Without APOE and CLU, neurons cannot properly regulate lipids, which accumulate in droplets that may impair neurons' abilities to communicate with each other.

The researchers verified their lab-based results by examining natural genetic variation in SORL1 expression in the brain tissue of 50 members of the cohorts, finding again that lower SORL1 activity in neurons was correlated with reduced APOE and CLU in these people.

The researchers are continuing to study other pathways that may lead to AD, such as those involving microglia (brain cells that perform immune functions). By using study models and techniques reflective of AD presentation in the [general population](#), the researchers hope to identify additional biological pathways important in AD.

"Our study is one of the first with [human cells](#) from a large collection of

individuals to try to understand the 'molecular road' that starts with SORL1, which we now see converges with APOE," Young-Pearse said.

"Our research points to the importance of developing interventions that target these and other molecular roads to Alzheimer's disease. The more we can understand subtype-specific differences in AD, the better we will be able to design rational therapeutic interventions to try to fix the problem that is primarily driving disease in each patient."

More information: Tracy L. Young-Pearse, Cell-type-specific regulation of APOE and CLU levels in human neurons by the Alzheimer's disease risk gene SORL1, *Cell Reports* (2023). [DOI: 10.1016/j.celrep.2023.112994](https://doi.org/10.1016/j.celrep.2023.112994). [www.cell.com/cell-reports/full...2211-1247\(23\)01005-7](http://www.cell.com/cell-reports/full...2211-1247(23)01005-7)

Provided by Mass General Brigham

Citation: Stem cell research sheds light on new 'molecular road' to Alzheimer's disease (2023, August 22) retrieved 28 April 2024 from <https://medicalxpress.com/news/2023-08-stem-cell-molecular-road-alzheimer.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.