Potential link for Alzheimer's disease and common brain disease that mimics its symptoms

August 19 2020

Credit: Unsplash/CC0 Public Domain

Alzheimer's disease is one of the most common causes of dementia, and while most people might know someone who is affected by it, the

genetic factors behind the disease are less known. A new study by investigators from Brigham and Women's Hospital uncovered a group of closely related genes that may capture molecular links between Alzheimer's disease and Limbic-predominant Age-related TDP-43 Encephalopathy, or LATE, a recently recognized common brain disorder that can mimic Alzheimer's symptoms. LATE is often combined with Alzheimer's disease to cause a more rapid cognitive decline. The study's results are published in *Neuron*.

"Genetic variants that regulate other genes' expressions are thought to play an important role in human disease, but genome-wide discovery of these variants has been difficult given the large numbers of genes and genetic variants that have to be tested," said Philip De Jager, MD, Ph.D., formerly of the Brigham. De Jager is now the chief of the Division of Neuroimmunology at Columbia University and senior author of the study. "We decided to leverage a previously developed data-driven approach to group closely correlated genes together into gene modules so that we can focus on the expression of 47 gene modules, rather than targeting more than 13,000 individual brain-expressed genes."

Gene expression is the process in which the information encoded in a gene is used to assemble a protein. The investigators conducted a genome-wide screen of genetic variants that regulate gene expression using 494 autopsied brain samples from the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP), community-based clinical-pathologic studies of aging and Alzheimer's disease. They observed that two genes, named TMEM106B and RBFOX1, regulate gene expression in the aging brain. The research team replicated their finding in an independent dataset from the Mayo RNAseq study, and analyzed clinical, autopsy, and genetic data to connect their findings with brain diseases that cause dementia.

The authors note that the study mainly analyzed people whose average

age was close to 90 at their time of death and brain donation. Therefore, the study results should be interpreted cautiously outside of this context, and further studies are required to investigate whether their findings could be extended to other TDP-43 related conditions that affect younger patients, such as frontotemporal dementia and amyotrophic lateral sclerosis.The research team also found that amyloid-β accumulation, a hallmark of Alzheimer's disease, and the TMEM106B risk variant both increased the expression of the same set of genes that are important in the function of lysosome, a cell compartment specializing in cellular waste removal. In turn, the increased expression of lysosomal genes correlated with LATE neuropathological change in human brain.

"It is becoming increasingly apparent that the frequent coexistence of Alzheimer's disease and LATE is not a coincidence," said Hyun-Sik Yang, MD, of the Division of Cognitive and Behavioral Neurology at the Brigham, who is the first author of the study. "We should further investigate the shared molecular links between Alzheimer's and LATE, so that one day we can treat and even prevent two of the most common causes of dementia in our rapidly aging population."

More information: Hyun-Sik Yang et al, Genetics of Gene Expression in the Aging Human Brain Reveal TDP-43 Proteinopathy Pathophysiology, *Neuron* (2020). DOI: 10.1016/j.neuron.2020.05.010

Provided by Brigham and Women's Hospital