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Key mechanism for a common form of Alzheimer's disease discovered

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Scientists from the Icahn School of Medicine at Mount Sinai, in collaboration with researchers from Icelandic Heart Association, Sage Bionetworks, and other institutions, have discovered that a network of genes involved in the inflammatory response in the brain is a crucial mechanism driving Late Onset Alzheimer's Disease (LOAD). The findings, published online today in the journal *Cell*, provide new understanding of key pathways and genes involved in LOAD and valuable insights to develop potential therapies for the disease.

To date, scientists have been challenged in understanding LOAD, the most common form of AD. Despite decades of intensive research, the causal chain of mechanisms behind LOAD has remained elusive. Currently, no effective disease modifying or preventive therapies exist and the number of Americans suffering from LOAD is expected to double by 2050.

The scientists performed an integrated analysis of the DNA of 376 deceased patients with LOAD, along with gene expression data (how the genes operate), to reveal the interconnected relationships among a large network of genes that drive the key pathways (the mechanisms) of the disease. The study authors created a biological network model, a complex mathematical representation of large amounts of data. These networks provide a unified map that integrates not only the key genes involved in the disease but also the biological pathways that those genes control. This network model provides a novel, comprehensive understanding of Alzheimer's disease and identifies potential targets for

intervention.

The scientists identified a pathway involving an inflammatory gene, TYROBP, that had not been previously implicated in Alzheimer's disease. TYROBP is known to interact with TREM2, another gene recently discovered to be involved in Alzheimer's by Rita Guerreiro, University College London, and Thorlakur Jonsson, deCODE Genetics, et al. Thus, the new paper draws attention to the TREM2-TYROBP pathway playing a central role in driving common forms of Alzheimer's disease.

"Defining the precise steps of the inflammatory response crucial to causing Alzheimer's disease has been elusive. We are pleased to discover these novel insights into that process," said Bin Zhang, PhD, the lead author of the study and an Associate Professor of Genetics and Genomic Sciences at Mount Sinai. "As a next step, we will evaluate drugs that impact the TREM2-TYROBP pathway as potential therapies for the disease. This discovery enables us to design more specific compounds that target these key steps precisely, in contrast to existing anti-inflammatory drugs that may be less ideal for hitting this target. "

Eric Schadt, PhD, an author of the study and Director of the Icahn Institute for Genomics and Multiscale Biology, and Chair of the Department of Genetics and Genomic Sciences at Mount Sinai, said "Creating a predictive model of Alzheimer's disease is a landmark achievement, yielding valuable insights into the complex mechanism of the disease. In the same way that sophisticated predictive mathematical models drive decision making in the global financial markets (what stocks to buy, how long to hold, when to sell, etc.), our field of medical research has begun to rely on network models such as this to derive meaning from vast amounts of patient data, enabling better understanding and treatment of human disease."

Jun Zhu, PhD, Professor of Genetics and Genomic Sciences at Mount Sinai and also an author of the new study, stated "This paper in *Cell*, along with recent discoveries, provides unequivocal proof that inflammation plays a central role in Alzheimer's disease, which is a consistent theme among common complex diseases that also include obesity and type II diabetes." Valur Emilsson, PhD, Head of Systems Medicine at Icelandic Heart Association and also a senior author of the paper, added, "Currently, we see a long lag time between appearance of amyloid on brain scans of patients and the appearance of clinical symptoms. An individual's inflammatory response could well play a role in the disease progression, and an appropriate anti-inflammatory drug, given after amyloid is detected but before symptoms begin, could be an important part of dementia prevention."

More information: *Cell*, Zhang et al.: "Tracing Multi-System Failure in Alzheimer Disease to Causal Genes."

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