New Alzheimer's treatment targets identified

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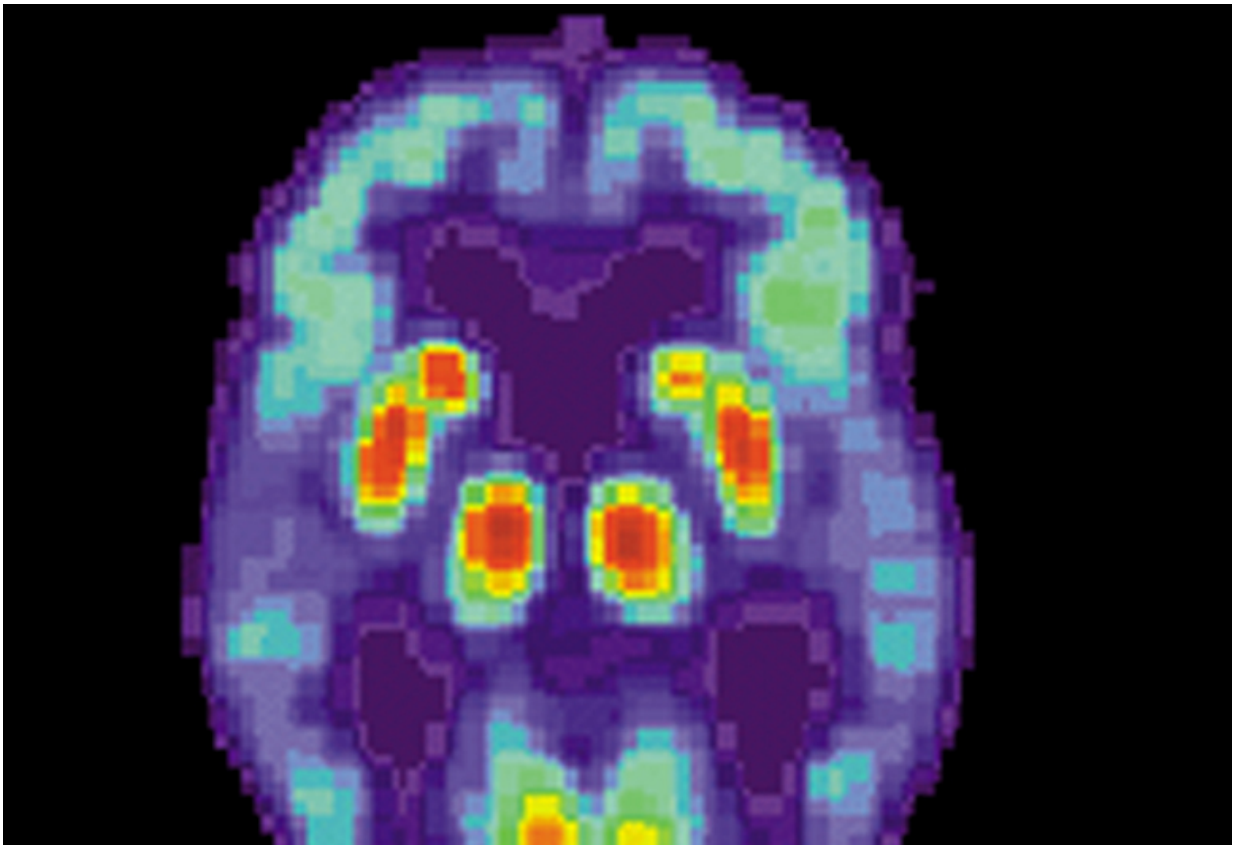

PET scan of a human brain with Alzheimer's disease. Credit: public domain

A research team at Washington University School of Medicine in St. Louis has identified potential new treatment targets for Alzheimer's disease, as well as existing drugs that have therapeutic potential against these targets.

The potential targets are defective proteins that lead to the buildup of amyloid in the brain, contributing to the onset of problems with memory and thinking that are the hallmark of Alzheimer's. The 15 existing drugs identified by the researchers have been approved by the Food and Drug Administration (FDA) for other purposes, providing the possibility of clinical trials that could begin sooner than is typical, according to the researchers.

In addition, the experiments yielded seven drugs that may be useful for treating faulty proteins linked to Parkinson's disease, six for stroke and one for amyotrophic lateral sclerosis (ALS). The new study, funded by the National Institute on Aging of the National Institutes of Health (NIH), is published July 8 in the journal *Nature Neuroscience*.

Scientists have worked for decades to develop treatments for Alzheimer's by targeting genes rooted in the disease process but have had little success. That approach has led to several dead ends because many of those genes don't fundamentally alter proteins at work in the brain. The new study takes a different approach, by focusing on proteins in the brain, and other tissues, whose function has been altered.

"In this study, we used human samples and the latest technologies to better understand the biology of Alzheimer's disease," said principal investigator Carlos Cruchaga, Ph.D., the Reuben Morriss III Professor of Neurology and a professor of psychiatry. "Using Alzheimer's disease samples, we've been able to identify new genes, druggable targets and FDA-approved compounds that interact with those targets to potentially slow or reverse the progress of Alzheimer's."

The scientists focused on protein levels in the brain, cerebrospinal fluid and blood plasma of people with and without Alzheimer's disease. Some of the proteins were made by genes previously linked to Alzheimer's risk, while others were made by genes not previously connected to the

disease. After identifying the proteins, the researchers compared their results to several databases of existing drugs that affect those proteins.

"They are FDA-approved, and all of the safety data on the drugs is available," said Cruchaga, . "With what is already known about the safety of these drugs, we may be able to jump directly to clinical trials."

Cruchaga said the team's focus on protein levels in key tissues has certain advantages over prior efforts to identify genes linked to Alzheimer's.

"The classic genetic studies of Alzheimer's have attempted to correlate genetic mutations with disease, but we know that genes carry the instructions to build proteins and that diseases such as Alzheimer's occur when those protein levels get too high or too low," Cruchaga explained. "To understand the biology of Alzheimer's disease, we should look at proteins rather than only at genes."

As an example, Cruchaga pointed to the APOE gene, which was first linked to Alzheimer's risk decades ago. But even after all this time, it still has not clear how that gene contributes to the disease.

"In this study, we were able to see that APOE alters levels of several proteins in brain tissue and CSF," Cruchaga said. "We also saw changes in proteins linked to another gene called TREM2 that was associated with Alzheimer's risk more recently. Understanding how the protein levels are affected by these risk genes is helping us to identify pathways that lead to disease."

Past research has helped identify about 50 genetic signals linked to Alzheimer's, but only a handful of the genes responsible for those signals have been found. Cruchaga said that focusing on protein levels in tissue may help reveal what's happening with the other 40-plus genetic signals

that appear to be connected to Alzheimer's risk.

The researchers analyzed proteins and genes from brain tissue, cerebrospinal fluid and blood plasma from samples gathered from 1,537 people in the U.S. The samples are stored at the Knight Alzheimer's Disease Research Center at Washington University. Half of the samples came from people with a clinical diagnosis of Alzheimer's disease; the other half came from study participants who are considered cognitively normal.

The researchers measured protein levels in the samples from the brain, CSF and plasma. Using statistical techniques, they then connected the protein levels to disease. There were 274 proteins linked to disease in study subjects' CSF, 127 in blood plasma and 32 in brain tissue.

They applied those findings and machine learning techniques to distinguish among the protein differences and zero in on some of the proteins that contribute to damage that leads to Alzheimer's.

"We have targets—although I'm not saying all of these targets are going to work or that all of the compounds we identified are going to stop the progress of the disease—but we have a real hypothesis," Cruchaga said. "And we expect it may be possible to move from these genetic studies into real clinical trials quickly. That's a big jump."

More information: Genomic atlas of the proteome from brain, CSF and plasma prioritizes proteins implicated in neurological disorders, *Nature Neuroscience* (2021). DOI: 10.1038/s41593-021-00886-6 , www.nature.com/articles/s41593-021-00886-6

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