New leads on treating dementia and Alzheimer's

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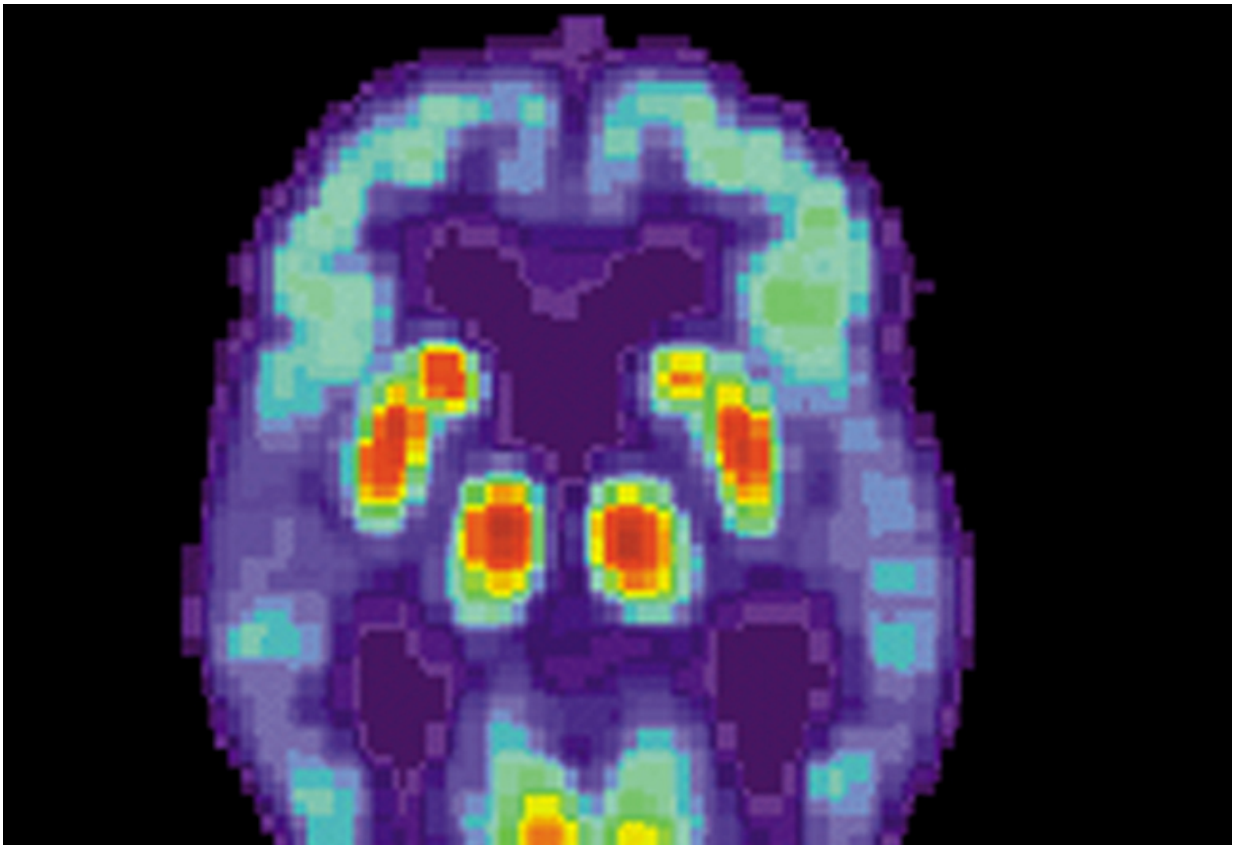

PET scan of a human brain with Alzheimer's disease. Credit: public domain

A new study by scientists in Australia and the US provides an explanation for why clinical trials of drugs targeting proteins in the brain that were thought to cause dementia and Alzheimer's have failed. The

study has opened the way for potential new treatments with existing drugs.

Published online in the journal *Human Molecular Genetics*, the researchers assembled evidence from a wide range of human studies and animal models of dementia-related diseases to show that inflammation is a major cause, not just a consequence.

They show that many genes linked with dementia regulate our susceptibility and response to inflammatory damage.

"For decades, scientists have thought that dementia and Alzheimer's Disease are caused by protein aggregates forming in the brain. But recent clinical trials of drugs that reduce the aggregates have failed," says project leader Professor Robert Richards, from the University of Adelaide's School of Biological Sciences. He is working in collaboration with the University's Adelaide Medical School and the National Institutes of Health, in the US.

Inflammation has long been known to increase as dementia-related diseases progress, but only now is it identified as the cause. Previously it was thought to act simply to clean up tissue damage caused by the protein aggregates.

"We know that inflammation has different phases – early on it can be protective against a threat by actively degrading it, but if the threat is not removed, then persistent inflammation actually causes cell death," says Professor Richards.

The new work turns previous thinking around. The genetic linkages imply that the inflammation comes first – and the tissue damage second.

"Many genes linked with dementia operate at the level of controlling

cellular inflammation. Both internal and external triggers interact with these genes to play a part. Inflammation is the point through which many triggers converge," says Professor Richards.

He likens the brain inflammation to a virus infection. "Inflammation is a very effective defence against foreign agents like viruses. But as we get older and accumulate mutations, our cells can make proteins and DNA products that mimic viruses, and these build up in the system," he says.

"Normally, our cells bar-code their own products to tell them apart from foreign agents. When these bar-codes aren't in place, our cells can't properly distinguish 'self' and 'non-self' trigger molecules. The result is inflammation that escalates and spreads – hence the term autoinflammatory disease."

Certain types of gene mutation cause these systems to fail earlier or more often, and can increase as we age – possibly accounting for age-related increased risk of developing dementia. The good news is that by reducing some elements of inflammation, it may be possible to reduce dementia symptoms.

"With this new understanding of the disease, we now need to test existing anti-inflammatory drugs for their effectiveness in treating dementia," he says.

More information: Robert I Richards et al. Neurodegenerative diseases have genetic hallmarks of autoinflammatory disease, *Human Molecular Genetics* (2018). DOI: 10.1093/hmg/ddy139

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