

Could new discovery play a role in diagnosing Alzheimer's earlier?

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Scientists have detected that a previously overlooked gene behavior could potentially lead to a new way to diagnose Alzheimer's earlier.

Published in the journal *Epigenetics*, an international research team's findings—discovered in mice and confirmed in human samples—suggest that the gene Presenilin1 (PSEN1) should be monitored as a 'biomarker': to see what environmental triggers, such as lifestyle and nutrition, can influence [brain](#) function and neurodegeneration or/and to see how well the body responds to a treatment for the disease.

Led by Professor Andrea Fuso at the Sapienza University of Rome, the study is the first to observe that the methylation (when the DNA activity of a gene can change, without changing the actual DNA sequence) of the gene PSEN1 is a common feature of Alzheimer's.

The results of the study appear to show that PSEN1, which was already known to behave differently for people with Alzheimer's, may have been dismissed in previous studies due to methods used to investigate DNA methylation.

The limitations of comparing results from mouse models and humans include, mouse stages of development and neurodegeneration not corresponding precisely to those of human aging. In this study, the team note that the blood and brain samples were obtained from different subjects. They suggest that future studies should analyse DNA from the same individuals, and in a larger cohort, in order to validate this potential biomarker.

However, Professor Fuso, from the Department of Experimental Medicine, at Sapienza University of Rome, states that the new results do offer "an exciting new area of investigation".

"We've detected an early sign of the disease in a DNA modification, or epigenetic marker, that was previously overlooked, and that could even provide a starting point for developing new therapies, as well as earlier

diagnosis" he added.

Worldwide, nearly 50 million people have Alzheimer's or related dementia. Yet, only 1-in-4 people with Alzheimer's disease have been diagnosed.

The earlier Alzheimer's can be detected, the better the chance of using treatment to delay the onset of severe dementia. Epigenetic alternations to [genes](#), induced by environmental triggers such as lifestyle and nutrition, can influence [brain function](#) and neurodegeneration. Evidence from animal models has found that changes to regulation of the PSEN1 gene is associated with Alzheimer's-like pathology, but only a handful of studies have investigated DNA modification of the gene in humans.

For the current study, the authors analysed patterns of DNA modification that affect the expression of the PSEN1 gene during brain development and during the progression of Alzheimer's in mice. They checked the results in humans by analysing post-mortem human brain tissue from Alzheimer's patients and from prenatal and postnatal babies and adolescents. To see whether changes to DNA methylation could be detected in human blood, they analysed blood samples from 20 patients with late-onset Alzheimer's disease, comparing the results to 20 healthy controls.

In Alzheimer's-prone mice of both sexes, they found that the PSEN1 gene was overexpressed. In adult female mice only, this overexpression was associated with lower DNA methylation. The results from post-mortem human brain tissue found upregulation of the PSEN1 gene in Alzheimer's patients. In both sexes, there was a significant inverse relationship between the extent of gene expression and DNA methylation. The fact that sex-specific differences were not found in human tissue could be due to the relatively small sample size.

"Differences between the sexes in DNA modifications would be extremely interesting to researchers working to better understand Alzheimer's disease and to develop new therapies," says Professor Fuso.

The analysis of blood samples was able to detect lower PSEN1-related DNA methylation in Alzheimer's patients compared to controls. The difference was significant, although not as large as in brain samples. As lower methylation was detectable in the blood, and is associated with higher expression of PSEN1, it could offer a new way to diagnose Alzheimer's early, and less invasively, than sampling brain tissue.

Professor Fuso concludes: "Our results offer an exciting new area of investigation, deploying the methods we used to study DNA methylation so that modifications won't be missed. If found to be causal, our findings would provide a starting point for developing epigenetic therapies."

More information: Noemi Monti et al, CpG and non-CpG Presenilin1 methylation pattern in course of neurodevelopment and neurodegeneration is associated with gene expression in human and murine brain, *Epigenetics* (2020). [DOI: 10.1080/15592294.2020.1722917](https://doi.org/10.1080/15592294.2020.1722917)

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