

Researchers identify gene involved in neuronal vulnerability in Alzheimer's disease

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Early stages of neurodegenerative disorders are characterized by the accumulation of proteins in discrete populations of brain cells and the degeneration of these cells. For most diseases, this selective vulnerability

pattern is unexplained, yet it could yield major insight into pathological mechanisms.

Alzheimer's disease (AD), the world-leading cause of dementia, is defined by the appearance of two hallmark pathological lesions, [amyloid plaques](#) (extracellular aggregates of A β peptides) and [neurofibrillary tangles](#) (intracellular aggregates of hyperphosphorylated tau, or NFTs). While plaques are widespread in the neocortex and hippocampus, NFTs follow a well-defined regional pattern that starts in principal neurons from the [entorhinal cortex](#).

In a new study from Boston University Chobanian & Avedisian School of Medicine, researchers have identified a gene they believe may lead to the degeneration of the neurons that are most vulnerable to AD.

"We are trying to understand why certain neurons in the brain are particularly vulnerable during the earliest stages of AD. Why they accumulate and degenerate very early is unknown. We believe elucidating this vulnerability would allow for a new therapeutic avenue for AD," said corresponding author Jean-Pierre Roussarie, Ph.D., assistant professor of anatomy & neurobiology at the school.

In collaboration with leading computational genomic experts from Rice University, the BU researchers, along with co-corresponding author Patricia Rodriguez-Rodriguez, Ph.D., from Karolinska Institute, used cutting-edge analysis tools with machine learning to identify the gene DEK as possibly responsible for the vulnerability of entorhinal cortex neurons.

They injected viruses into the entorhinal cortex of experimental models and neurons grown in the lab to manipulate levels of the DEK gene.

When they reduced the levels of the DEK gene, vulnerable neurons started to accumulate tau and degenerate.

According to the researchers, preventing these neurons from degeneration by targeting DEK or proteins that collaborate with DEK would prevent patients from developing [memory loss](#) and would curtail the disease before it spreads to larger areas of the brain. "Given that entorhinal cortex neurons are necessary for the formation of new memories, and since they are so vulnerable and the first to die, this explains why the first symptom of AD is the inability to form new memories," said Roussarie.

The researchers believe these findings are the first step in understanding how these fragile neurons die, yet they hope to uncover additional genes to fully understand what leads to the death of critical memory-forming neurons.

The research is [published](#) in the journal *Brain*.

More information: Patricia Rodriguez-Rodriguez et al, A cell autonomous regulator of neuronal excitability modulates tau in Alzheimer's disease vulnerable neurons, *Brain* (2024). [DOI: 10.1093/brain/awae051](#)

Provided by Boston University School of Medicine

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