Researchers discover how mutations in presenilin gene cause early onset Alzheimer's disease

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Researchers have discovered how mutations in the presenilin 1 gene cause early-onset Alzheimer's disease (AD). The finding, reported online in the journal *Cell*, opens the door to developing novel treatments for this form of the mind-robbing disease and for the more common, late-onset form that develops later in life and affects millions of people worldwide.

The presenilin gene is most commonly associated with the early-onset familial form of Alzheimer's, which runs in families and can strike people in their 30s. The gene was discovered 15 years ago, but until now no one understood how mutations in the gene caused the disease.

The researchers led by Ralph Nixon , MD, PhD, professor in the Departments of Psychiatry and Cell Biology at NYU Langone Medical Center and director of the Center for Dementia Research at the Nathan S. Kline Institute for Psychiatric Research, discovered that the presenilin 1 gene performs a crucial biological function that enables cells to digest unwanted proteins and is essential for brain cell survival. The mutations, they report, disrupt this cellular protein-recycling process, killing nerve cells.

"In mouse models of Alzheimer's disease and in skin cell of patients with Alzheimer's disease caused by presenilin mutations, we observed that the ability to break down and reuse normal proteins and to remove potentially toxic damaged proteins and organelles is severely impaired," says Dr. Nixon who is also director of the Center of Excellence on Brain Aging and the Silberstein Alzheimer's Institute at NYU Langone Medical Center. The impairment can kill nerve cells, and the loss of neurons does not appear to be dependent on amyloid beta, the plaque-forming protein found in the brains of patients.

"Most of the drug development for Alzheimer's has been focused on removing amyloid from the brain," says Dr. Nixon. "Our findings strongly suggest that there are alternative pathways that can be targeted as well. For example, therapies could be aimed at repairing the cellular mechanism that eliminates toxic proteins before they damage the brain."

Preliminary observations from ongoing studies at the Nathan Kline Institute, says Dr. Nixon, indicate that similar disruptions of the cellular protein-recycling process occur in neurons affected by late-onset Alzheimer's, suggesting that factors other than mutations in the presenilin gene can also impair this process.

More than 160 rare mutations in the presenilin 1 gene and two others have been found to cause early-onset familial Alzheimer's disease. Only a few genes associated with late-onset form of Alzheimer's, the most common form of senile dementia, have been identified so far.

"Presently, no effective treatment exists to either slow or prevent the progression of Alzheimer's disease," says Dr. Nixon. "There is urgent need to see Alzheimer's disease as multi-factorial and to approach the treatment from that perspective."

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