Alzheimer's treatment may be more effective for people at highest risk

Joanna E Pankiewicz
Jairo Baquero-Buitrago
Sandrine Sanchez
Jennifer Lopez-Contreras
Jungsu Kim
Patrick M. Sullivan
David M. Holtzman
Martin J. Sadowski

Video Abstract

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Abstract

There may be a silver lining for those at high risk for Alzheimer's: as the chance of getting the disease goes up, certain treatments may become more effective. The risk of developing Alzheimer's largely relies on a gene called APOE, with different variants conferring more or less risk. Usually, having a high-risk allele is bad news, but a group of researchers from New York University has reported that carrying the high-risk allele could actually boost responsiveness to immunotherapy, a promising new treatment option. The APOE gene helps determine how much beta-amyloid accumulates in the brain. Beta-amyloid starts as small misfolded bits of protein that clump together to form the plaques that are the hallmark of Alzheimer's. As the plaques appear, the brain deteriorates, particularly in regions associated with memory. One way to potentially halt this process is to use antibodies that recognize beta-amyloid. The antibodies bind to the protein and signal to the immune system to clear it out. Because the amount of amyloid-beta depends on a person's APOE genotype, the researchers wanted to find out whether genotype could also predict how well someone responds to treatment. They did this by making mice with different human variants of the APOE gene. Then, they treated the animals either with an antibody against beta-amyloid or a control antibody. All of the mice responded well to the beta-amyloid antibody. But the mice with the high risk allele showed the greatest reduction of beta-amyloid, thanks to higher activation of immune cells in the brain known as microglia. In other words, the mice with the most severe disease were also the most responsive to treatment. Although the relationship between APOE genotype and immunotherapy responsiveness must still be examined in humans, these findings open a hopeful new chapter for patients at the highest risk of Alzheimer's.