

# Why do some people with Alzheimer's disease die without cognitive impairment?

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Since the time of Dr. Alois Alzheimer himself, two proteins (beta-amyloid (A $\beta$ ) and tau) have become tantamount to Alzheimer's disease (AD). But a Mayo Clinic study challenges the perception that these are the only important proteins accounting for the clinical features of the devastating disease.

In a large clinico-imaging pathological study, Mayo Clinic researchers demonstrated that a third [protein](#) (TDP-43) plays a major role in AD pathology. In fact, people whose brain was TDP positive were 10 times more likely to be cognitively impaired at death compared to those who didn't have the protein, showing that TDP-43 has the potential to overpower what has been termed resilient brain aging. The study was published in the journal *Acta Neuropathologica*.

Mayo Clinic researchers studied brains of 342 patients who had died with pathologically confirmed AD and divided them into two groups based on the presence or absence of the protein TDP-43. The protein was found in 195 or 57 percent of the cases.

"We wanted to determine whether the TDP-43 protein has any independent effect on the clinical and neuroimaging features typically ascribed to AD and we found that TDP-43 had a strong effect on cognition, memory loss and medial temporal atrophy in AD," says Mayo Clinic neurologist Keith Josephs, M.D., the study's lead investigator and author. "In the early stages of the disease when AD pathology was less severe, the presence of TDP-43 was strongly associated with cognitive impairment. Consequently, TDP-43 appears to play an important role in the cognitive and neuroimaging characteristics that have been linked to AD."

The study also found that patients who suffered from greater [cognitive impairment](#) and medial temporal atrophy at the time of death had greater TDP-43 burden and had the protein in a greater

number of brain regions.

"This is why we believe that TDP-43 pathology could help shed light on the phenomenon of resilient cognition in AD and explain why some patients remain clinically normal, while others do not, despite both having similar degrees of AD pathology," says Dr. Josephs. "Our findings suggest that in order to have AD and be cognitively resilient, TDP-43 must be absent, so it should be considered a potential therapeutic target for the future treatment of AD."

**More information:** "TDP-43 is a key player in the clinical features associated with Alzheimer's disease," Keith A. Josephs, Jennifer L. Whitwell, Stephen D. Weigand, et al, *Acta Neuropathologica* March 2014

Provided by Mayo Clinic

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