

Predicting vulnerability to Alzheimer's disease and delirium

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Marked by acute temporary confusion, disorientation and/or agitation, postoperative delirium is the most common post-surgical complication in older adults, striking as many as half of adults older than 65 who undergo high-risk procedures such as cardiac surgery or hip replacements. Postoperative delirium is also tightly linked to Alzheimer's disease (AD). Although each can occur independently, Alzheimer's is a leading risk factor for delirium, and an episode of delirium puts patients at increased risk for cognitive decline and Alzheimer's disease. However, the physiological mechanisms linking delirium and Alzheimer's disease remain largely unknown.

A paper published today in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, researchers at Beth Israel Deaconess Medical Center (BIDMC) shed new light on a [genetic risk factor](#) for Alzheimer's disease that may indirectly influence patients' risk of postoperative delirium. In a study of [older adults](#) without dementia undergoing major non-[cardiac surgery](#), researchers observed that patients carrying a specific variant of a gene appeared to be much more vulnerable to delirium under certain conditions than people without this genetic variant. The team's findings could open the door to future interventions to prevent or mitigate postoperative delirium in at-risk patients.

"Our findings confirmed our hypothesis that patients' risk of postoperative delirium differs by genetic predisposition," said Sarinnapha M. Vasunilashorn, Ph.D., an Assistant Professor of Medicine in the Division of General Medicine at BIDMC. "We observed a strong and significant association between high postoperative inflammation and delirium incidence, duration and severity among patients carrying a variant of the gene considered to be risky, while the association was weaker and non-significant among non-carriers."

Vasunilashorn and colleagues focused on a gene called APOE (short for apolipoprotein E). The risky version of the gene—notated as APOE $\epsilon 4$ —is the strongest known genetic risk factor for late-onset Alzheimer's disease and a widely studied genetic risk marker for delirium. While recent studies have shown no direct relationship between APOE $\epsilon 4$ and delirium, Vasunilashorn's team hypothesized that the gene variant might indirectly influence risk of delirium by modifying the body's response to inflammation—part of the immune system's natural defense system—indicated by the presence of an inflammatory marker in the blood called CRP (C-reactive protein).

Using data from the Successful Aging after Elective Surgery (SAGES) study, an ongoing prospective cohort study investigating risk factors and

long-term outcomes of delirium, the scientists looked at the incidence, severity and duration of delirium in 560 patients 70 years or older who underwent major non-cardiac surgeries under general or spinal anesthesia. Patients were monitored for delirium, assessed by daily cognitive assessments of patients' attention, memory and orientation throughout their hospital stay.

Analyzing data from patients' blood (drawn before surgery, immediately after surgery, two days after and one month after) revealed that, among carriers of the APOE ϵ 4 gene variant, patients with high levels of inflammation had an increased risk of [postoperative delirium](#). However, among non-carriers of the APOE ϵ 4 gene variant, the scientists found no such association.

"Our findings suggest that APOE ϵ 4 may be an indicator of brain vulnerability," said Vasunilashorn, who also holds appointments at Harvard Medical School, and the Harvard T.H. Chan School of Public Health. "This work may inform the targeting of future interventions, such as anti-inflammatory treatments, for prevention of [postoperative delirium](#) and its associated adverse long-term cognitive outcomes in patients with this genetic susceptibility."

More information: Sarinnapha M. Vasunilashorn et al, Apolipoprotein E genotype and the association between C-reactive protein and postoperative delirium: Importance of gene-protein interactions, *Alzheimer's & Dementia* (2019). [DOI: 10.1016/j.jalz.2019.09.080](#)

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