NPTX2 protein may predict mild cognitive impairment years before symptoms, study suggests

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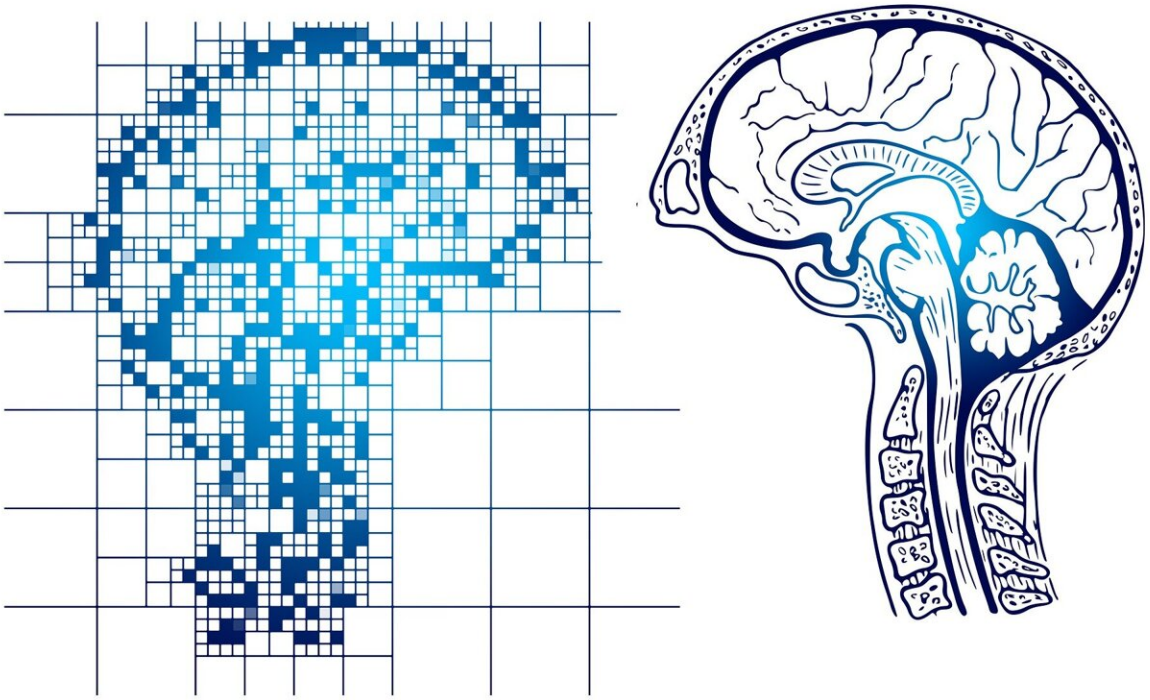

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Results of a long-term study of cognitively healthy adults—most with a family history of Alzheimer's disease—have added to evidence that low

spinal fluid levels of a protein linked to learning and memory in mice may serve as an early predictor of mild cognitive impairment (MCI) years before symptoms appear.

The findings, which may potentially offer new targets for treating or preventing Alzheimer's and other dementias, showed that a relatively low level of the protein known as NPTX2 is not only a likely standalone risk factor for MCI and Alzheimer's dementia, but also improves prediction of cognitive impairment after accounting for levels of traditional biomarkers and well-established genetic risk factors for Alzheimer's.

The study, conducted by Johns Hopkins Medicine scientists on more than 250 primarily middle-aged adults, the vast majority of whom were white, concluded that the findings were consistent with and expand prior studies by establishing that measurements of NPTX2 in cerebrospinal fluid were predictive of MCI onset within or even beyond seven years before symptoms occurred.

A report on the study was published July 25 in the *Annals of Neurology*.

According to the Alzheimer's Association, MCI, marked by mild memory loss or challenges with other cognitive processes, such as language or executive function, affects up to 18% of people age 60 and older. People with MCI maintain most normal daily activities, but are known to be at higher risk of Alzheimer's disease or other forms of dementia.

It is estimated that 6.7 million Americans age 65 and older are living with Alzheimer's dementia, with that number expected to double by 2050. The growing prevalence of dementias has given urgency to the search for better and earlier predictors, and targets for treatments that prevent or slow progression. At present, there is only one FDA-approved drug on the market known to even modestly slow symptoms of

Alzheimer's in its early stages, and there are no cures or preventives.

"Our research shows declining levels of NPTX2 occur many years prior to the emergence of MCI or Alzheimer's symptoms, which raises the possibility of developing new therapeutics that target NPTX2," says Anja Soldan, Ph.D., associate professor of neurology at the Johns Hopkins University School of Medicine and corresponding author of the study.

"Additionally, it appears that this protein is not a specific marker to just Alzheimer's, and these findings may be relevant to a variety of other neurodegenerative diseases. So if we can find ways of increasing levels of NPTX2, then it could be applied to identify early and possibly treat other types of memory loss or cognitive impairment as well."

For the study, which involved adults recruited by the National Institutes of Health and Johns Hopkins Medicine, researchers conducted baseline medical and cognitive exams on 269 cognitively normal individuals, and collected spinal fluid samples biannually.

The average age of participants at baseline was 57.7 years. Nearly all were white, 59% were female, most were college educated and 75% had a close relative with Alzheimer's. NPTX2 levels were measured, as well as the main abnormal proteins found in patients with Alzheimer's, namely beta-amyloid, total tau and phosphor-tau. Subjects underwent clinical and cognitive assessments for an average of 16 years.

Results showed:

- Over time, 77 subjects progressed to MCI or dementia within or after seven years of baseline measurements. Of those participants, 88% were diagnosed with Alzheimer's as a primary or secondary cause of dementia.

- Those who progressed to MCI had on average of about 15% lower levels of NPTX2 at baseline compared with those who remained unimpaired, a difference that remained significant after accounting for baseline Alzheimer's biomarker levels and genetic factors.
- Higher levels of baseline tau and phosphor-tau levels were associated with greater decreases in NPTX2 over time, suggesting that NPTX2 may decline in response to tau pathology.

"Currently, we only have drugs that modify mild symptoms of Alzheimer's disease and nothing right now to give people who are cognitively normal but at higher risk," Soldan emphasized. But when and if that changes, Soldan adds, having an accurate way to predict such risk will play a large role in targeting treatments.

Soldan also cautioned that "we're a long way out" from a simple way to routinely test spinal fluid samples for NPTX2 levels, and further research is needed to determine what factors alter the protein's levels. Potential root causes could be genetics, lifestyle factors or a combination of them.

Soldan also underscored the new study's limitations, including the racial and educational makeup of the study population.

Additional authors include Marilyn Albert (principal investigator of the BIOCARD study, from which these data were derived), Sungtaek Oh, Taekyung Ryu, Corinne Pettigrew, Yuxin Zhu, Abhay Moghekar, Mei-Fang Xiao, Gregory Pontone, Chan-Hyun Na and Paul Worley from the Johns Hopkins University School of Medicine.

More information: Anja Soldan et al, NPTX2 in Cerebrospinal Fluid Predicts the Progression From Normal Cognition to Mild Cognitive Impairment, *Annals of Neurology* (2023). DOI: 10.1002/ana.26725

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