# Protein changes identified in early-onset Alzheimer's

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(Medical Xpress) -- With a lack of effective treatments for Alzheimer's, most of us would think long and hard about whether we wanted to know years in advance if we were genetically predisposed to develop the disease. For researchers, however, such knowledge is a window into Alzheimer's disease's evolution.

Understanding the biological changes that occur during the clinically "silent" stage — the years before symptoms appear — provides clues about the causes of the disease and may offer potential targets for drugs that will stop it from progressing.

In a new study, researchers at UCLA have identified chemical changes taking place in the brains of people destined to develop familial Alzheimer's disease at least 10 years before symptoms or diagnoses occur. Reporting in the current online edition of the journal Archives of Neurology, John Ringman, a UCLA associate professor of neurology, and colleagues identified changes in 56 proteins, including increases in the amyloid protein long associated with Alzheimer's, inflammatory markers and other proteins related to the brain's synapses, the connections between neurons through which these brain cells communicate with each other.

Familial Alzheimer's and sporadic, late-onset Alzheimer's are distinct forms of what many consider a single disease. The majority of Alzheimer's cases are sporadic and late-onset, developing after age 65; the causes of this disease type are not completely understood but are at

least partly genetic. Familial Alzheimer's (FAD), a rare form of the disease caused by certain gene mutations, affects less than 2 percent of patients. It is typically early-onset, developing before age 65, and it is inherited — all offspring in the same generation have a 50–50 chance of developing FAD if one of their parents had it.

For this study, researchers developed protein profiles drawn from the cerebrospinal fluid of 14 FAD mutation carriers and compared them with five related non-carriers. In all, they identified 56 proteins that showed significant differences between carriers and non-carriers. Fourteen of these proteins had been reported in prior studies on late-onset Alzheimer's (including APP, transferrin and other inflammatory markers), but many others were unique to this study, including calsyntenin 3, AMPA 4 glutamate receptor and osteopontin. Normally, these proteins are thought to play a role in the growth and remodeling of synapses, and their alteration in pre-symptomatic Alzheimer's may represent an early manifestation of the loss of these critical structures.

"Unfortunately, we do not yet have effective medications to stop the progression of Alzheimer's," said Ringman, who works at UCLA's Mary S. Easton Center for Alzheimer's Disease Research. "In this study, we've identified chemical changes occurring in the brains of persons destined to develop Alzheimer's disease 10 years or more prior to the expression of symptoms. By studying the cerebrospinal fluid of persons developing Alzheimer's disease at a relatively young age with cutting-edge protein chemical techniques, we found changes in markers reflecting inflammation as well as the breakdown of synapses.

"This provides potential new targets for drug interventions, and it helps elucidate the degree to which FAD and late-onset Alzheimer's are similar and to what degree they are distinct. Such knowledge may ultimately allow us to tailor our treatments to individuals, depending on the 'type' of Alzheimer's they have."

The study, funded in part by the pharmaceutical company Pfizer Inc., a grant from the state of California and other sources, was performed at UCLA's Easton Center, one of 10 centers currently receiving funding from the state. State funding helps these centers provide specialized care for patients with Alzheimer's disease and other forms of dementia and their families, and it enables the centers to provide training for those engaged in the diagnosis and care of patients with dementia in California.

Additional study authors included Gregory Cole, Sophie Sokolow, Karen Gylys, Daniel H. Geschwind, Jeffrey L. Cummings and Hong I. Wan from UCLA; Howard Schulman, Chris Becker and Ted Jones from Caprion Proteomics U.S.; and Yuchen Bai and Fred Immermann from Pfizer Inc.

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