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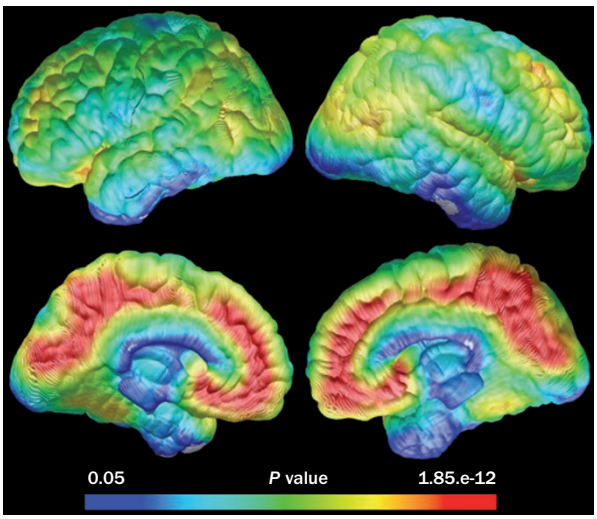
ALZHEIMER DISEASE

New insights into preclinical Alzheimer disease

Recent failures of drugs in phase III trials in patients with mild to moderate Alzheimer disease (AD) have highlighted a potential need for earlier intervention. Now, two studies in people with a genetic mutation that causes early-onset AD have shed light on changes in the CNS that accompany the preclinical phase of disease.



Statistical map showing significantly greater cortical-to-pontine florbetapir uptake in 30 *PSEN1* mutation carriers relative to noncarriers. Image courtesy of A. Fleisher.

The studies involved members of the Colombian Alzheimer's Prevention Initiative Registry—a well-defined kindred that includes approximately 1,500 people with a dominantly inherited Glu280Ala mutation in the presenilin 1 (*PSEN1*) gene, which causes AD by age 50 years. "Studying this cohort provides an opportunity to better understand the preclinical pathology of individuals who we know will develop clinical manifestations of AD," says Adam Fleisher, lead author of one of the papers.

Fleisher *et al.* used florbetapir PET imaging to measure brain levels of fibrillar amyloid-β (Aβ) in 11 symptomatic individuals, 19 presymptomatic mutation carriers, and 20 asymptomatic noncarriers from the Colombian kindred. "We were able to use a cross-sectional study design to emulate longitudinal changes, as disease progression is highly associated with age in this kindred," explains Fleisher.

Mutation carriers showed greater florbetapir binding in the brain than did age-matched noncarriers, in a pattern that matched Aβ deposition in the more-common, late-onset form of AD. Fibrillar Aβ began to accumulate around 16 years before the median age of onset of mild cognitive impairment (MCI) and about 21 years before the median age of dementia onset, with Aβ levels rising steeply for approximately 9 years, before reaching a plateau 6 years before MCI onset. "These findings advance our understanding of fibrillar Aβ biomarker changes associated with preclinical and clinical stages of AD, in preparation for preclinical treatment trials," says Fleisher.

In the other study, Eric Reiman, Yakeel Quiroz and colleagues focused on young adult (18–26-year-old) members of the Colombian kindred, and found that Glu280Ala mutation carriers had elevated cerebrospinal fluid (CSF) Aβ levels compared with noncarriers. "This result is consistent with the idea that early-onset AD involves Aβ overproduction prior to the reduction in CSF Aβ that occurs in conjunction with amyloid deposition," explains Reiman. Structural and functional MRI scanning revealed that even at this young age, mutation carriers had reduced grey matter volume and different patterns of neural activation during cognitive tasks compared with noncarriers. "The findings in young adults provide further evidence of brain changes prior to biomarker evidence of amyloid deposition in people at risk of AD," says Reiman. "These advances could help to set the stage for a new era in AD prevention research," he concludes.

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Original articles Fleisher, A. S. *et al.* Florbetapir PET analysis of amyloid-β deposition in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional study. *Lancet Neurol.* doi:10.1016/S1474-4422(12)70227-2 | Reiman, E. M. *et al.* Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case–control study. *Lancet Neurol.* doi:10.1016/S1474-4422(12)70228-4