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LONGITUDINAL CHANGE IN CSF BIOMARKERS IN A PRESYMPTOMATIC CARRIER OF AN *APP* MUTATION

Persons inheriting fully penetrant autosomal dominant mutations causing familial Alzheimer disease (AD) provide the opportunity to characterize presymptomatic biomarker changes in a population where studies might be performed to efficiently identify preventative interventions. Decreased $A\beta_{42}$ and increased total tau (t-tau) and phosphorylated tau (p-tau) in CSF are associated with incident¹ and established AD.² These markers have been increasingly incorporated as outcome measures for clinical trials, but further characterization of their natural course is necessary to interpret such studies. Though longitudinal changes in these markers are expected for individuals developing AD, such changes have yet to be thoroughly documented prospectively. Here we report changes in AD CSF biomarkers over time in a presymptomatic carrier of the V717I mutation in the amyloid precursor protein (*APP*) gene.³

Methods. Due to confidentiality issues, the gender and chronological age of this individual are not disclosed. As the age of disease onset can be consistent within families harboring this *APP* mutation,³ we report the individual's age relative to the median age of dementia diagnosis within their family. The subject was enrolled in a UCLA institutional review board–approved study of persons at risk for familial AD in which participants undergo in-depth clinical, genetic, and biochemical assessments. CSF was collected and stored in polypropylene tubes. Samples were centrifuged and the supernatant stored at -80°C . Initial and follow-up samples were later analyzed for t-tau, p-tau₁₈₁, and $A\beta_{42}$ levels using Innogenetics INNO-BIA AlzBio3 multiplex assays on standardized xMAP Luminex technology in duplicate in the same run. The interassay coefficient of variation reported by the manufacturer is 7.7%, which was verified in a storage stability study. The presence of the V717I substitution in *APP* was assessed with direct sequencing. Clinical assessment including comprehensive neuropsychological

testing and the Clinical Dementia Rating (CDR) scale were performed blind to mutation status.

Results. At the time of the initial lumbar puncture (LP), the participant was 22 years younger than the median age of dementia diagnosis within the family, performed within normal limits on neuropsychological testing, and scored 0 on the CDR. The second LP was performed 4.5 years later, at which time neuropsychological performance remained stable and CDR remained 0. Longitudinal CSF analyses indicated that $A\beta_{42}$ levels decreased from 683.8 pg/mL to 575.6 pg/mL (-16%), t-tau levels increased from 88.3 pg/mL to 107.6 pg/mL ($+22\%$), and p-tau₁₈₁ levels increased from 30.8 pg/mL to 48.8 pg/mL ($+58\%$). Corresponding values of $A\beta_{42}$, t-tau, and p-tau₁₈₁ in 5 nonmutation carrying family members enrolled in the same study from whom CSF was obtained and assays performed in an identical manner (mean adjusted age 6 years prior to dementia diagnosis) were 618.4 pg/mL (SEM = 44.8), 50.5 pg/mL (SEM = 4.2), and 24.6 pg/mL (SEM = 4.1). Therefore, in the 4.5-year interval between LPs, $A\beta_{42}$ fell from the high to low range of normal. t-Tau was already elevated at baseline and at follow-up both t-tau and p-tau₁₈₁ levels had increased to levels above those of persons not carrying familial AD mutations.

Discussion. We previously demonstrated decreased $A\beta_{42}/A\beta_{40}$ ratios and increased t-tau and p-tau₁₈₁ in CSF from presymptomatic familial AD mutation carriers⁴ with virtually no overlap between tau levels in mutation carriers and noncarriers. Cross-sectional differences in $A\beta_{42}$, t-tau, and p-tau₁₈₁ levels between controls and patients with AD are well-documented.² However, longitudinal changes in these biomarkers have not been consistently reported in prior studies and recent work indicates these measures remain relatively stable over intervals of up to 2 years in mild cognitive impairment (MCI) and AD.⁵ A recent study in persons without dementia (mean age 73 years) found that though baseline CSF $A\beta_{42}$, t-tau, and p-tau₁₈₁ levels were not related to cognitive function, decreasing CSF $A\beta_{42}$ and increasing p-tau₁₈₁ levels over 4 years' time were associated with

cognitive decline.⁶ Furthermore, the *APOE* $\epsilon 4$ allele was associated with greater decreases in $A\beta_{42}$ and increases in t-tau. Another study found stability of CSF $A\beta_{42}$ and t-tau levels among cognitively normal subjects, persons with MCI, and persons with AD over a 1-year period except for a modest increase in t-tau in elderly controls (mean age 75).⁷

Our findings indicate that CSF biomarker changes occur early during the presymptomatic state in familial AD and we found substantial changes between 22 and 17 years before the expected onset of dementia. Though persons carrying familial AD mutations allow one to sensitively identify the time course of biomarker changes during the presymptomatic period, the degree to which these findings can be generalized to late-onset AD is unclear. Verification of our results with larger numbers of subjects awaits larger studies such as those of the Dominantly Inherited Alzheimer Network (<http://www.dian-info.org/>).

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INTERLEUKIN-7 RECEPTOR ALPHA GENE POLYMORPHISM INFLUENCES MULTIPLE SCLEROSIS RISK IN ASIANS

A recent genome-wide survey identified non-human leukocyte antigen (*HLA*) genes that are related to multiple sclerosis (MS). Among these, an association of a single nucleotide polymorphism (SNP), rs6897932, in the interleukin-7 receptor α gene (*IL-7RA*) with MS susceptibility has been widely replicated in Caucasians.^{1–3} The SNP located in the transmembrane domain of IL-7R α is nonsynonymous and functional: the MS-susceptible CC allele increases levels of the soluble form of IL-7R α via exon skipping, and decreases the expression of membrane-bound IL-7R α , thereby causing decreased IL-7/IL-7R signaling.^{1–3} IL-7/IL-7R signaling induces thymic production of FOXP3⁺ regulatory T cells, which efficiently ameliorate experimental autoimmune encephalomyelitis,⁴ an animal model of MS.

Thus, the rs6897932 polymorphism of the IL-7RA gene may confer MS susceptibility through decreased production of FOXP3⁺ regulatory T cells due to downregulated IL-7/IL-7R signaling. This polymorphism has never been reported in either MS or neuromyelitis optica (NMO) in Asians. Therefore, in the present cross-sectional study, we investigated the association of the IL-7RA SNP rs6897932 with non-NMO MS and NMO in the Japanese.

Methods. All patients with NMO fulfilled the 2006 Wingerchuk⁵ criteria for NMO, while those with NMO spectrum disorders who did not completely meet the criteria were excluded. All non-NMO patients with MS satisfied the revised McDonald criteria for MS⁶ but did not meet the Wingerchuk criteria for NMO. All patients were thoroughly examined in the Neurology Departments of the University Hos-