Genetic and Environmental Moderation Among Plasma-Based Biological Markers of Alzheimer’s Disease

Matthew S. Panizzon¹²; Robert A. Rissman³; Jeremy A. Elman¹²; Nathan Gillespie⁴; Michael C. Neale⁴; Chandra Reynolds⁵; Michael Lyons⁶; Carol E. Franz¹²; and William S. Kremen¹²

¹Department of Psychiatry, University of California San Diego
²Center for Behavior Genetics of Aging, University of California San Diego
³Department of Neuroscience, University of California San Diego
⁴Virginia Institute for Psychiatric and Behavioral Genetics
⁵Department of Psychology, University of California Riverside
⁶Department of Psychological and Brain Sciences, Boston University

KEYWORDS: beta amyloid, tau, neurodegeneration, genetic moderation, Alzheimer’s disease

ABSTRACT:

The current research framework for Alzheimer’s disease (AD) defines the condition in terms of the progressive accumulation of beta-amyloid (Aβ) and tau, as well as progressive neurodegeneration. This framework represents a biological definition of AD, and shifts AD research toward examining younger cohorts where the progression of biological markers can be examined prior to dementia onset. The genetic analysis of these biomarkers is still in its infancy, as little is known regarding their genetic and environmental determinants, or if the magnitude of genetic and environmental influences change over disease progression. The goal of the present study was to determine whether plasma-based Aβ, tau, and neurodegeneration – assessed by neurofilament light (NFL) – moderated the genetic and environmental determinants of one another. Data were from the Vietnam Era Twin Study of Aging. The average age at assessment was 67.1 years (SD=2.6). Using a bivariate model for the analysis of gene-environment interaction, we found evidence for significant genetic and environmental moderation across multiple biomarkers. All variance components of Aβ₄₂, for example, significantly increased as a function of NFL level, resulting in a change in heritability from .26 to .47. A similar pattern of moderation was observed between tau and Aβ₄₂. The heritability of Aβ₄₂ also increased as a function of Aβ₄₀, a more abundant form of the peptide, while the genetic correlation between them decreased. These results suggest that the degree to which AD biomarkers are influenced by genetic and environmental factors is in part dependent on disease staging as indexed by biomarker accumulation.

GRANT SUPPORT: R01 AG050595, R01 AG023381, R01 AG056410, P01 AG055367, and K01 AG063805