Gene Expression Biomarkers for Early Identification of Mild Cognitive Impairment: A Twin Study

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Principal Investigators

TSUANG, MING T.

Institution

UNIVERSITY OF CALIFORNIA SAN DIEGO

Contact information of lead PI
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Gene Expression Biomarkers for Early Identification of Mild Cognitive Impairment: A Twin Study

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NIH (NIA)

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1

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Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Behavioral and Social Science... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Epidemiology And

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Research Abstract
Both the NIH and the NIA-Alzheimer's Association have emphasized the importance of early identification beginning in midlife to predict Alzheimer's disease (AD) and cognitive decline. Two keys to early identification are accurate detection of mild cognitive impairment (MCI), which can be a precursor of AD, and identification of biomarkers of MCI risk with potential for screening large populations. We have shown that blood-based transcriptomic signatures accompany and, in some cases, predict the development of some psychiatric illnesses, and others have recently found the same for MCI and AD. However, existing cross-sectional case- control biomarker studies of MCI were not designed to illuminate whether peripheral blood transcriptome biomarkers are precursors, concomitants, or consequences of MCI, and they are unable to shed light on the relative influence of inherited and environmental factors on each component of the putative biomarker signature. This is important because MCI and AD are both partially heritable disorders. Our proposed project would address these pressing questions within the context of an ongoing study that was explicitly designed to allow such inferences: our longitudinal Vietnam Era Twin Study of Aging (VETSA). The VETSA, just beginning wave 3 of longitudinal data collection from 1151 twins, began studying subjects at an average age of 56 (range: 51-60). The mean age of subjects in VETSA 3 will be 67; thus it will provide data both before and during the key transition from midlife to early old age. A large twin sample with a narrow age range that has been longitudinally characterized for many years on multiple domains (cognitive, physiological, psychological, biomedical, and genetic) makes VETSA uniquely well suited to characterizing individual differences in cognitive aging with a focus on MCI, beginning in midlife. The present proposal seeks to expand our ability to detect MCI early in VETSA subjects in a highly efficient and cost-effective manner by integrating transcriptome measurements from peripheral blood cells into the existing VETSA 3 protocol. We propose to collect an additional blood sample from all subjects in VETSA 3, extract and sequence RNA from those samples, and merge these transcriptome measures with the other data collected in VETSA to pursue three Specific Aims as part of a new VETSA Gene Expression (VETSA-GEX) project: 1) Construct an atlas of genetic and environmental influences in expression levels of all RNA transcripts (including both coding mRNAs and short and long non-coding RNAs) and gene co-expression networks detected in peripheral blood at midlife; 2) Discover, replicate, and functionally characterize peripheral blood transcriptomic signatures of neuropsychologically defined MCI and MCI severity, both by non-twin analysis of the entire sample and by co- twin-control analysis; and 3) Integrate peripheral blood transcriptome measures with other putative MCI biomarkers already being measured on these twins, including plasma ?-amyloid (A?) and phosphorylated-tau (p-tau) levels, genetic risk scores, and psychophysiological measures such as task-evoked pupil dilation.

Lay Summary
Alzheimer's disease and mild cognitive impairment are major and growing public health problems, imposing tremendous costs at personal, social, and institutional levels. One strategy for combating these disorders is to improve our ability to detect their presence or predict their emergence, so that earlier interventions can be developed, by discovering objective, laboratory-based biomarkers. This project seeks to identify blood-based gene-expression biomarkers of MCI within the context of an ongoing longitudinal study of middle to early old- age twins, which will help us understand to what degree the molecular correlates or precursors of MCI are influenced by genetic and environmental factors, as well as the biological processes that may

underlie this condition.

Further information available at:

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United States of America

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