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Featured Article

A genetics-based biomarker risk algorithm for predicting risk of Alzheimer's disease

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Abstract

Introduction: A straightforward, reproducible blood-based test that predicts age-dependent risk of Alzheimer's disease (AD) could be used as an enrichment tool for clinical development of therapies. This study evaluated the prognostic performance of a genetics-based biomarker risk algorithm (GBRA) established on a combination of apolipoprotein E (*APOE*)/translocase of outer mitochondrial membrane 40 homolog (TOMM40) genotypes and age, then compare it to cerebrospinal fluid (CSF) biomarkers, neuroimaging, and neurocognitive tests using data from two independent AD cohorts.

Methods: The GBRA was developed using data from the prospective Joseph and Kathleen Bryan, Alzheimer's Disease Research Center study (n = 407; 86 conversion events [mild cognitive impairment {MCI} or late-onset Alzheimer's disease {LOAD}]). The performance of the algorithm was tested using data from the Alzheimer's Disease Neuroimaging Initiative study (n = 660; 457 individuals categorized as MCI or LOAD).

Results: The positive predictive values and negative predictive values of the GBRA are in the range of 70%–80%. The relatively high odds ratio (approximately 3–5) and significant net reclassification index scores comparing the GBRA to a version based on *APOE* and age alone support the value of the GBRA in risk prediction for MCI due to LOAD. Performance of the GBRA compares favorably with CSF and imaging (functional magnetic resonance imaging) biomarkers. In addition, the GBRA "high" and "low" AD-risk categorizations correlated well with pathologic CSF biomarker levels, positron emission tomography amyloid burden, and neurocognitive scores.

Discussion: Unlike dynamic markers (i.e., imaging, protein, or lipid markers) that may be influenced by factors unrelated to disease, genomic DNA is easily collected, stable, and the technical methods for measurement are robust, inexpensive, and widely available. The performance characteristics of the GBRA support its use as a pharmacogenetic enrichment tool for LOAD delay-of-onset clinical trials and merit further evaluation for its clinical utility in evaluating therapeutic efficacy.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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1. Introduction

It can take decades of undetected disease progression before frank symptoms of cognitive decline are diagnosed in Alzheimer's disease (AD) patients. Treatments that delay or even prevent AD dementia require robust prognostic biomarkers of the preclinical disease process for accurate patient selection into clinical trials. Effective biomarkers with reproducible performance characteristics that are relatively inexpensive can be used for enrichment of prevention trial cohorts and, perhaps, for subsequent identification of individuals most suitable for intervention.

To date, cerebrospinal fluid (CSF, amyloid-beta $[A\beta]_{1-42}$, total tau [t-tau], and phosphorylated tau [p-tau]) and neuroimaging biomarkers (structural/functional magnetic resonance imaging [fMRI] and amyloid-imaging) have been among the most studied biomarkers in individuals with prodromal AD symptoms (mild cognitive impairment [MCI]) or full AD dementia. These biomarker methods are currently the "gold standard" for biomarker-based risk prediction and their clinical utility is described in opinions of the International Working Group (IWG), National Institute of Aging-Alzheimer's Association (NIA-AA), European Medicines Agency (EMA), and Food and Drug Administration (FDA) [1–4]. However, CSF biomarkers suffer from the invasive nature of a lumbar puncture, issues with laboratory-to-laboratory variability and reproducibility, and a lack of globally recognized reference standards and cutoff values. In addition, neuroimaging methods require (1) specialized, expensive magnetic resonance imaging (MRI) and/or positron emission tomography (PET) scanning equipment that are only available at specific medical centers; (2) use of labile reagents; (3) specially trained medical personnel to administer the tests and interpret the results [5]; and (4) establishment of threshold/cutoff values meaningful for clinical observations.

Blood-based biomarkers have the potential to be easier to obtain and more economical; platforms to test these are widely available at medical facilities around the world. Unfortunately, there are multiple factors that can confound the measurement of RNA, protein, and/or metabolite levels in the blood and correlation with AD disease state, including diseases comorbid with AD, various medical treatments, and even diet. Strong prognostic biomarkers that can predict future onset of AD would ideally be dichotomous (marker positive/negative) and not continuously variable, i.e., where different analyte levels correspond to different risks and assignment of arbitrary cutoff values are imposed.

A simple, genetics-based biomarker risk algorithm (GBRA) using a combination of apolipoprotein E (*APOE*, ε2,ε3,ε4), translocase of outer mitochondrial membrane 40 homolog (TOMM40) rs10524523 variable length poly-T repeat polymorphism (TOMM40′523) genotypes, and age has been developed as a prognostic tool for assessing AD age-of-onset (AOO) in asymptomatic people [6]. In this study, we present data on the predictive characteristics of the GBRA to identify people at risk for MCI due to AD [7], and comparative data for CSF and neuroimaging (fMRI) based biomarkers, and neurocognitive testing. The overall hypothesis to be tested is that the combination of age, *APOE* genotype, and TOMM40′523 genotype, used in an algorithm based on historical MCI/AD AOO data, will outperform algorithms based on age alone or *APOE* genotype in predicting conversion from normal cognition to dementia (phenoconversion) when assessed by receiver operating curves (ROC) analysis or other well-defined statistical methods to compare biomarkers. Also compared are the categories for risk of phenoconversion with widely used biomarkers for AD including CSF-based biomarkers, Pittsburgh Compound B (PIB)-PET imaging of amyloid burden, and neurocognitive tests.

2. Methods

2.1. AD cohorts

The Joseph and Kathleen Bryan, Alzheimer's Disease Research Center (Bryan-ADRC) Memory, Health and Aging Study (MHA) cohort measured age of AD onset of subjects followed at the Bryan-ADRC at Duke University [8]. MHA participants included MCI patients from the Duke Memory Disorders Clinic and individuals who were enrolled in the Bryan-ADRC autopsy program as controls; some of these individuals have been followed for 10–20 years. The latter individuals were cognitively normal when they enrolled and many have progressed to AD or MCI. Study subjects were followed annually with the National Alzheimer's Coordinating Center-Unified Data Set (NACC-UDS) protocol and battery [9] of neuropsychological tests to monitor cognitive changes and diagnose onset of cognitive impairment and probable AD dementia. Importantly, the subjects were followed prospectively to capture the earliest clinical symptoms of the disease process and were all assessed using validated tests including the NACC-UDS, along with standardized practices and definitions of symptom onset and cognitive status at one research center, the Bryan-ADRC. Cases of