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Molecular markers of neuropsychological functioning and Alzheimer's disease

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Abstract

Background: The current project sought to examine molecular markers of neuropsychological functioning among elders with and without Alzheimer's disease (AD) and determine the predictive ability of combined molecular markers and select neuropsychological tests in detecting disease presence.
Methods: Data were analyzed from 300 participants (n = 150, AD and n = 150, controls) enrolled in the Texas Alzheimer's Research and Care Consortium. Linear regression models were created to examine the link between the top five molecular markers from our AD blood profile and neuropsychological test scores. Logistical regressions were used to predict AD presence using serum biomarkers in combination with select neuropsychological measures.
Results: Using the neuropsychological test with the least amount of variance overlap with the molecular markers, the combined neuropsychological test and molecular markers was highly accurate in detecting AD presence.
Conclusion: This work provides the foundation for the generation of a point-of-care device that can be used to screen for AD.

Keywords: Alzheimer's disease; Diagnosis; Biomarkers; Verbal fluency

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia and is estimated to cost the U.S. healthcare system nearly $1.1 trillion dollars by the year 2050 [1]. Because of the growing prevalence rate of AD and the increase in preventative healthcare measures, which enable individuals to live longer, it is believed that over 80% of those 65 years and more will experience cognitive decline associated with AD [1]. Thus the importance of identifying early AD symptoms has increased as the burden on the healthcare system continues to grow. Recent work has sought to establish a rapid and cost-effective means of identifying those with early AD, through creating a blood test to screen for disease presence [2–6].

Through this work, researchers have sought to provide utility for identifying blood-based biomarkers associated with neuropsychological functioning to establish biomarker profiles of disease states [7]. This effort termed Molecular Neuropsychology has identified biomarker profiles of neurocognitive functioning and begun combining select blood biomarkers with select cognitive assessments with the goal of establishing a point-of-care device for primary care settings that can be used to identify those with early AD [7,8]. This work has stemmed from the growing need for a rapid screening measure for those early in the disease process. These methods can also be used for screening in clinical trials.

Initial work by Ray and colleagues established an 18-plasma-based blood test to differentiate those with AD from those with normal cognition, with an overall accuracy of 89% [9]. This work was built on by O'Bryant and colleagues [2–4] who examined the implications of using

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serum-based biomarkers to create an algorithm to detect AD presence. In our most recent work, we generated a blood test based profile consisting of 21 serum proteins, which yielded an accuracy of 96% in identifying those with AD from those with normal cognition [4]. The top five serum proteins included in the blood-test were interleukin 5 (IL-5), IL-6, IL-7, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [4].

In our recent work, we demonstrated that combining two of the top five biomarkers (TNF-α and IL-7) with one neuropsychological measure (Clock 4-point), yielded excellent accuracy in detecting early AD [8]. Even for very early AD cases, this approach was able to provide an overall accuracy of 91% with a sensitivity of 97% and specificity of 72% [8]. This work has shown that combining neuropsychological screening measures with a limited number of biomarkers can increase the ability to identify those who are at a higher risk for the development of AD.

AD pathology has become increasingly linked with inflammation, specifically among Non-Hispanic whites [4,10,11]. IL-5, -6, and -7 were found to be some of the top serum-based proteins among individuals with AD [4]. Although inflammatory blood-based biomarkers have been established as predictors of AD presence, outside our laboratory, few studies to date have sought to examine how much variance is accounted for by the biomarkers themselves in relation to measures of cognition [7]. Given that these biomarkers are associated with AD, it is hypothesized that the markers will account for a significant amount of variance in memory scores. This project sought to examine molecular markers of neuropsychological functioning among elders with and without AD and sought to determine the predictive ability of combined molecular markers and select neuropsychological tests in detecting disease presence.

2. Methods

2.1. Participants

Data were analyzed from 300 participants (n = 150, AD and n = 150, normal cognition) enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC). The TARCC protocol has been well documented elsewhere [12,13]. Briefly, the methodology for the TARCC study includes having each participant undergo an annual standardized assessment at one of the six participating sites, which includes a medical evaluation, neuropsychological evaluation, a clinical interview, and a blood draw. The diagnosis of AD is based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [14] and healthy controls performed within normal limits on neuropsychological testing. All participants also had a Clinical Dementia Rating (CDR) assigned. Institutional Review Board approval was obtained at each site and written and informed consent was obtained.

2.2. Human serum sample collection

Nonfasting blood samples were collected in 10 ml of tiger-top tubes. The obtained serum samples were allowed to clot in a vertical position for approximately 30 minutes at room temperature. The samples are then centrifuged for 10 minutes at the speed of 1300 ×g within 1 hour of collection. Then 1.0 ml of aliquots of serum are transferred into cryovial tubes with Freezerworks™ barcode labels firmly affixed to each aliquot. Samples are then placed in −80°C freezer within 2 hours of collection for storage until use in an assay. Serum was assayed in duplicate via a multiplex biomarker assay platform using electrochemiluminescence (ECL) on the SECTOR Imager 2400A from Meso Scale Discovery (MSD; http://www.mesoscale.com). The MSD platform has been used extensively to assay biomarkers of AD [15,16]. ECL measures are considered to be more conventional than those of enzyme-linked immunosorbent assay, which are the current standard for most assays because of their increased sensitivity [15].

2.3. Neuropsychological testing

The core neuropsychology battery for the TARCC includes commonly used instruments for detection of AD in both clinical and in research settings. The battery includes the following tests: Trail-Making Test [17], Boston Naming Test (30- and 60-items versions) [18], verbal fluency (Controlled Oral Word Association Task [COWAT], Animals) [18], Clock-Drawing Test (4-points) [18], American National Adult Reading Test [18], digit span (Wechsler Adult Intelligence Scale-Revised, Wechsler Adult Intelligence Scale Third Edition, Wechsler Memory Scale-Revised [WMS-R]) [19], WMS Logical Memory and Visual Reproduction (WMS-R and WMS-III) [19], the Geriatric Depression Scale (GDS-30) [20], the Mini-Mental State Examination [21], and ratings on the CDR [22]. Scores were equated across versions by using scale scores as outcome variables in analyses.

2.4. Statistical analyses

Linear regression models were created to examine the link between the top five molecular markers from our AD blood profile [4] (IL-5, IL-6, IL-7, TNF-α, CRP) and neuropsychological test scores. Next, logistical regressions were used to predict AD presence using the serum biomarkers in combination with the select neuropsychological measures that were least related to the biomarker profile.

3. Results

Demographic characteristics of the TARCC samples are presented in Table 1. AD cases were found to be older ($P < .001$), have fewer years of education ($P = .003$) and be predominantly female ($P < .001$). Significant differences were also observed across the molecular markers used. Those with AD, were found to have higher levels of IL-7 ($P < .001$), TNF-α ($P < .001$), and IL-6 ($P < .001$) as