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Blood-Based Biomarkers

Thrombopoietin is associated with δ's intercept, and only in Non-Hispanic Whites

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Abstract

Introduction: Serum thrombopoietin (THPO) is a biomarker of Alzheimer's disease (AD) and the latent dementia phenotype, "δ". Both associations may be specific to non-Hispanic whites (NHW), not Mexican-Americans (MA). In this analysis, we examine ethnicity's effect on THPO's association with change in δ scores, in the Texas Alzheimer's Research and Care Consortium (TARCC).

Methods: We constructed an ethnicity equivalent δ homolog ("dEQ") among n = 1113 MA and n = 1958 NHW. dEQ was output as a composite "dEQ-score" for each of five annual TARCC waves. Those composites were used as indicators of a latent growth curve (LGC). The mean dEQ intercept (idEQ) and slope (ΔdEQ) were estimated in a random subset of N = 1528 participants and replicated in the remainder (n = 1544). THPO was regressed onto idEQ and ΔdEQ. Those associations were tested separately in MA and NHW.

Results: dEQ correlated strongly with CDR-SB (r = 0.99, $P < .001$) and achieved high AUCs for AD diagnosis at each wave (range = 0.95–0.99). THPO was significantly associated with idEQ but not ΔdEQ. That effect was observed in NHW only. In MA, THPO had no associations with either idEQ or ΔdEQ.

Discussion: We confirm THPO's ethnicity-specific association with δ in NHW. It is further clarified that this association is specific to δ's intercept and not its slope. This analysis provides a model for how dementia's specific serum biomarkers can be characterized.

Keywords: Aging; Cognition; Dementia; Functional status; Intelligence; THPO

1. Introduction

We have recently constructed a latent phenotype for dementia itself, as distinct from cognitive performance *per se* [1]. Our approach uses a novel confirmatory bifactor model in a structural equation model framework. Compared to observed measures, the latent variable "δ" (for dementia) is relatively free of demographic measurement bias, continuously distributed and appears to be "indifferent" to its cognitive indicators [2].

δ's indifference to its indicators suggests that it can be modeled in virtually any cognitive battery. We have demonstrated this down to the level of individual items [3]. Thus, we further distinguish between δ, that is, "the cognitive correlates of functional status", and "d," that is, δ's reification as a composite score in any specific cognitive battery. Across multiple batteries, these results in a set of δ homologs, all of which appear to share a similar psychometric profile.

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δ homologs accurately diagnose dementia and have been associated with Alzheimer's Disease (AD) neuropathology [4], AD-specific CSF biomarkers [5], certain serum inflammatory proteins [6], baseline, prospective change, and future CDR scores [7,8].

We recently demonstrated significant associations between δ and 10 serum proteins in the Texas Alzheimer's Research and Care Consortium (TARCC). They included thrombopoietin (THPO), platelet-derived growth factor, thrombospondin-1 (THBS1), and von-Willebrand factor [6]. THPO was the strongest. Its effect was comparable to education and *APOE* ε4, and stronger than age, yet independent of both. THPO was also the strongest predictor of clinical AD in O'Bryant et al.'s 2011 study [9]. That association was specific to AD in non-Hispanic whites (NHW) [10] but not in Mexican-Americans (MA) [11]. Similarly, THPO's association with δ scores was limited to NHW [6].

THPO regulates the proliferation and maturation of megakaryocytes and platelet production. However, δ is not related to vasculopathy-related biomarkers such as vascular cell adhesion molecule type 1 (VCAM-1), vascular endothelial growth factor, or homocysteine (HCY), nor is it associated with ischemic pathology (at autopsy) in the National Alzheimer's Coordinating Center [7]. Regardless, platelets have recently been recognized to contribute to innate immunity [12]. δ's serum biomarkers, in their aggregate, suggest that innate immunologic processes may be responsible for dementia severity as measured by δ [6].

The analyses to date have been cross sectional. However, δ's intercept and slope are independently associated with dementia severity, and δ's change over time is strongly related to change in dementia severity [7,8]. It remains to be determined whether THPO is associated with δ's slope, and whether their association remains specific to NHW in TARCC's rapidly expanding cohort.

2. Methods

2.1. Subjects

Subjects included n = 3072 TARCC participants: 1182 cases of AD, 611 "mild cognitive impairment" (MCI) cases, and 1276 controls. Each underwent serial annual standardized clinical examinations. Institutional review board approval was obtained at each site, and written informed consent was obtained from all participants.

2.2. δ's indicators

All tests were available in Spanish translation.

Logical memory II: [13] After a 30-minute delay, the subject recalls two paragraphs read aloud.

Visual reproduction I: [13] The subject immediately reproduces a set of figures after a brief exposure.

The Controlled Oral Word Association (COWA): [14] The patient is asked to name as many words as they can in 1 minute, beginning with a certain letter.

Digit Span Test (DST): [13] The DST sums the longest set of numbers that the subject can immediately recall in correct order (forward and backward).

Instrumental activities of daily living (IADL): [15] IADL's were assessed using informant ratings. Functional abilities were rated on a Likert scale ranging from 0 (no impairment) to 3 (specific incapacity). A total IADL score calculated as the sum of all eight items.

2.3. Clinical covariates

Education: Education was coded continuously as years of formal education.

Ethnicity: Ethnicity was determined by self-report and coded dichotomously as "Hispanic" and "non-Hispanic".

Gender: Gender was coded dichotomously.

2.4. Clinical correlates

The Clinical Dementia Rating Scale sum of boxes (CDR): [16] The CDR estimates dementia severity. A clinician rates the participant on six domains—memory, orientation, judgment and problem solving, community affairs, home, and hobbies and personal care. Each is rated on a scale of 0.0–3.0. A total CDR "sum of boxes" (CDR-SB) score is summed across all domains.

2.5. Biomarkers

TARCC's methodology has been described elsewhere [17]. Briefly, nonfasting blood samples were collected in serum-separating tubes, allowed to clot at room temperature for 30 minutes, centrifuged, aliquoted, and stored at −80°C in plastic vials. Serum samples were sent frozen to rules-based medicine (RBM) (http://www.rulesbasedmedicine.com/) in Austin, TX. There, they were assayed without additional freeze-thaw cycles. RBM conducted multiplexed immunoassay via their human multianalyte profile (human MAP).

3. Statistical analyses

3.1. Analysis sequence

Data were inspected for normality and outliers (e.g., values >3 standard deviations) using univariate kurtosis and skewness statistics. Multicolinearity was assessed by noting the correlation among observed variables and the variance inflation factor (VIF) [18]. Multivariate normality in the structural models was assessed using Mardias coefficient [19].

The structural models were performed using Analysis of Moment Structures (AMOS) software [20]. The maximum likelihood estimator was chosen. Observed indicators were adjusted for age, education, ethnicity, and gender. The residual covariances between these variables were estimated if they were significant and improved fit.