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DIAGNOSTIC ASSESSMENT & PROGNOSIS

Proteomic profiles of prevalent mild cognitive impairment and Alzheimer's disease among adults with Down syndrome

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Abstract

Introduction: We sought to determine if a proteomic profile approach developed to detect Alzheimer's disease (AD) in the general population would apply to adults with Down syndrome (DS).

Methods: Plasma samples were obtained from 398 members of a community-based cohort of adults with DS. A total of n = 186 participants were determined to be non-demented and without mild cognitive impairment (MCI) at baseline and throughout follow-up; n = 50 had prevalent MCI; n = 42 had prevalent AD.

Results: The proteomic profile yielded an area under the curve (AUC) of 0.92, sensitivity (SN) = 0.80, and specificity (SP) = 0.98 detecting prevalent MCI. For detecting prevalent AD, the proteomic profile yielded an AUC of 0.89, SN = 0.81, and SP = 0.97. The overall profile closely resembled our previously published profile of AD in the general population.

Discussion: These data provide evidence of the applicability of our blood-based algorithm for detecting MCI/AD among adults with DS.

KEYWORDS

blood based, biomarkers, plasma, Down syndrome, Alzheimer's disease

1 | INTRODUCTION

Down syndrome (DS) is one of the most common genetic disorders, occurring in 1:700 births.[1] Many individuals with DS are now living well into adulthood due to advances in early life interventions and medication. Advancing age places those with DS at increased risk for Alzheimer's disease (AD) as most adults with DS will develop AD-associated neuropathology such as amyloid beta (Aβ) plaques by the age of 40.[2] The neuropathological manifestations of AD among individuals with DS has been attributed, at least in part, to triplication and overexpression of the amyloid precursor protein (APP) located on chromosome 21.[3] However, there is a wide range regarding age at onset for AD in adults with DS, and similar to the general population AD presents as a complex disease with dysfunction across multiple pathways.

Current and highly accurate methods for detecting both Aβ and tau pathology include cerebrospinal fluid (CSF) and positron emission tomography (PET) scans. These diagnostic modalities, however, are highly invasive procedures and are also very costly. As has been proposed for AD,[4] and is the case for cancer,[5] there is a need for a multi-tiered assessment process for detecting and predicting AD risk among adults with DS for novel therapeutic and preventative trials in order to improve clinical outcomes. Such a multi-tiered method would reduce participant burden while resulting in cost-containment by only conducting confirmatory diagnostic procedures on those with highest likelihood of positivity. It is important to note that the purpose of the blood-based biomarker is not "diagnostic" but rather as the first step in a multiple-step screening process.

Over the years, there has been a significant effort devoted toward the identification of blood-based biomarkers associated with prevalent and incident AD in adults with DS.[6-10] Initial work conducted among 108 adults with DS and 64 cognitively normal controls using enzyme-linked immunosorbent assay (ELISA) methods found elevated plasma Aβ 1-42 among those with one *APOE* ε4 allele.[6] This same study revealed an association between increased Aβ 1-42 and risk of prevalent dementia (odds ratio [OR] = 1.76, 95% confidence interval [CI] 1.1-2.7). In a follow-up study[7] among 204 adults with DS, those non-demented adults with DS who were in the middle and highest quartiles of plasma Aβ 1-42 were over two times as likely to develop AD as compared to those in the lowest quartile. Those in the highest quartile of Aβ 1-42 were also found to have an increased risk for mortality.[7,11]

Additional work conducted by this same group[12] revealed that changes in Aβ 1-42 and Aβ 1-40 over time could provide biological insight into dementia risk. Findings showed that declines in Aβ 1-42 and in the Aβ 1-42/Aβ 1-40 ratio, along with an increase in Aβ 1-40, were associated with increased risk of dementia.[12] Coppus et al.[13] examined plasma Aβ 1-40 and Aβ 1-42 among n = 506 adults with DS and found that those in the highest concentrations of Aβ 1-40 and Aβ 1-42 were at increased risk for incident dementia.

Others have also shown correlations between CSF and brain levels of Aβ and tau protein and dementia status in adults with DS.[14,15] Fortea et al.[16] found that CSF but not plasma Aβ was correlated with AD. This same group went on to examine the diagnostic accuracy of individual plasma biomarkers in distinguishing those with and without AD in adults with DS and found that levels of Aβ 1-40, Aβ 1-42, and total tau (t-tau) independently produced lower rates of detection when compared to levels of neurofilament light chain (NfL). Moreover, levels of plasma NfL alone were shown to better predict risk for AD as compared with a combination of plasma and CSF biomarkers (plasma Aβ1-42; Aβ1-40, CSF Aβ1-42:t-tau, or CSF Aβ1-42:phosphorylated tau [p-tau]) (receiver-operating characteristic [ROC] curve = 0.95 vs 0.53-0.74, respectively).[16] Additional work examining other individual plasma biomarkers found that a number of inflammatory-based markers including precursor of the neurotrophin nerve growth factor (proNGF), mitochondrial processing peptidase 1 (MPP-1), MMP-3, MMP-9, interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-8, and IL-10 were higher among individuals with DS and AD.[17]

Our group has generated and cross-validated a blood-based proteomic profile that is highly accurate in detecting AD in the general population.[18-22] In addition, in our recent work, we have shown that our proteomic profile approach can detect and discriminate among additional neurodegenerative diseases (eg, Parkinson disease, dementia with Lewy bodies).[20,23,24] In addition, our proteomic profile approach for AD is heavily weighted for inflammatory markers. Given the literature documenting inflammatory dysfunction associated with AD among adults with DS, here we sought to determine if our

RESEARCH IN CONTEXT

1. Systematic review: Literature was identified and reviewed using PubMed. Several articles described growing effort to identify blood-based biomarkers associated with Alzheimer's disease (AD) among adults with Down syndrome (DS). Recent work has generated and cross-validated a blood-based proteomic profile in detecting AD and mild cognitive impairment (MCI) in the general population. No such work has sought to apply this same proteomic profile in detecting MCI and AD among adults with DS.
2. Interpretation: Our findings show that the previously establish blood-based proteomic profile for prevalent AD could be effectively applied among adults with DS with 87% accuracy. When examining prevalent MCI among adults with DS, the applied proteomic profile was found to be 95% accurate.
3. Future directions: This article provides evidence that comparable accuracy rates can be obtained using an established blood-based proteomic profile for MCI and AD among adults with DS. Further studies are needed to explore and refine the necessary number and type of blood-based biomarkers for increased accuracy of detection in this at-risk population.

proteomic profile approach could be applied to detect AD in adults with DS.

2 | METHODS

2.1 | Subjects

The study cohort included 398 members of a community-based cohort of adults with confirmed DS from work previously described.[9-11,25] All individuals were 30 years of age or older at study onset and resided in New York, New Jersey, Pennsylvania, or Connecticut. In all cases, a family member or correspondent provided informed consent with participants providing assent. Recruitment, informed consent, and study procedures were approved by the institutional review boards of Columbia University Medical Center, the New York State Psychiatric Institute, and the New York State Institute for Basic Research in Developmental Disabilities.

2.2 | Clinical assessment

Assessments were repeated at 14- to 18-month intervals over five cycles of data collection and included evaluations of cognition and functional abilities, behavioral/psychiatric conditions, and health status. Cognitive function was evaluated with a test battery designed for use with individuals with DS varying widely in their levels of intellectual functioning, as described previously.[26] Structured interviews were conducted with caregivers to collect information on changes in cognition, function, adaptive behavior, and medical status. The past and current medical records of all participants were reviewed.

2.3 | Classification of dementia

The classification of dementia status, dementia subtype, and age at onset was determined during clinical consensus conferences, where information from all available sources were reviewed. We classified participants into three groups, following the recommendations of the American Association of Mental Retardation and the International Association for the Scientific Study of Intellectual Disability (AAMR-IASSID) Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability.[27,28] Participants were classified as nondemented if they were without cognitive or functional decline. Participants were classified as having mild cognitive impairment (MCI) if they showed some cognitive and/or functional decline that was not of significant magnitude to meet dementia criteria. Participants were classified as demented if there was a history of progressive memory loss, disorientation, and functional decline over a period of at least 1 year, and if no other medical or psychiatric conditions that might result in or mimic dementia were present (eg, stroke).

2.4 | Apolipoprotein E genotype (APOE)

APOE genotyping was carried out by polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) analysis using *Hha*I (*Cfo*I) digestion of an *APOE* genomic PCR product spanning the polymorphic (cys/arg) sites at codons 112 and 158, followed by acrylamide gel electrophoresis to document the restriction fragment sizes.[29] Participants were classified according to the presence or absence of at least one *APOE* $\varepsilon 4$ allele

2.5 | Proteomics

Plasma samples were shipped to the Institute for Translational Research (ITR) Biomarker Core for proteomic assays. Automation of the proteomic assay preparation was conducted using a customized Hamilton Robotics StarPlus system. This automated liquid-handling workstation substantially improves reliability of assays preparation, which reduces error and coefficient of variation (CVs) and provided increased quality assurance and quality control (QA/QC) monitoring. Any re-aliquot needs were conducted via the Hamilton easyBlood robotic system. Proteomic assays were conducted using a multi-plex biomarker assay platform using electrochemiluminescence (ECL) lab using the QuickPlex from Meso Scale Discovery (MSD) per our methods published previously.[20,21] The MSD platform has been used extensively to assay biomarkers associated with a range of human diseases including AD.[30-33] ECL technology uses labels that emit light when electronically stimulated, which improves the sensitivity of detection of many analytes at very low concentrations. ECL measures have well-established properties of being more sensitive and requiring less volume than conventional ELISAs,[32] the gold standard for most assays. As reported previously, the analytic performance of each of these markers in our AD proteomic profile (listed below) is excellent.[21,23,24] A total of 500 μL of plasma was utilized to assay the following markers (including CV and lowest level of detection): fatty acid binding protein 3 (FABP3; CV = 4.2, LLOD = 206.8 pg/mL), β2 microglobulin (B2M; CV = 5.5, LLOD = 96.3 pg/mL), pancreatic polypeptide (PPY; CV = 5.5, LLOD = 3436.8 pg/mL), c-reactive protein (CRP; CV = 2.5; LLOD = 19.7 pg/mL), intercellular adhesion molecule 1 (ICAM-1; CV = 3.9; LLOD = 5.7 pg/mL), thrombopoietin (TPO; CV = 3.2; LLOD = 45.3 pg/mL), α2 macroglobulin (A2M; CV = 1.7; LLOD = 4284 pg/mL), exotaxin 3 (CV = 6.5; LLOD = 1.4 pg/mL), TNF-α (CV = 2.9; LLOD = 0.04 pg/mL), tenascin C (TNC; CV = 3.5; LLOD = 20.8 pg/mL), IL-5 (CV = 4.3; LLOD = 0.05 pg/mL), IL-6 (CV = 4.6; LLOD = 0.07 pg/mL), IL-7 (CV = 5.8; LLOD = 0.1 pg/mL), IL-10 (CV = 2.7; LLOD = 0.02 pg/mL), IL-18 (CV = 5.0; LLOD = 1.7 pg/mL), I309 (CV = 8.3; LLOD = 2.6 pg/mL), Factor VII (CV = 2.1; LLOD = 14.7 pg/mL), vascular cell adhesion protein 1 (VCAM-1; CV = 2.5; LLOD = 9.1 pg/mL), thymus and activation regulated chemokine (TARC; CV = 3.2; LLOD = 45.3 pg/mL), and serum amyloid A (SAA; CV = 3.6; LLOD = 21.3 pg/mL). As can be seen, analytic performance was excellent.

TABLE 1 Demographic characteristics for participants without cognitive or functional decline and those with prevalent MCI

Characteristic	Without cognitive/ functional decline	Prevalent MCI	*p*
N	186	50	
Age (mean ± SD)	48.6 ± 6.7	53.6 ± 5.3	<.001
Gender, N (%)			
Male	44 (23.7)	16 (32.0)	.23
Female	142 (76.3)	34 (68.0)	
Level of intellectual disability, N (%)			
Mild/moderate	127 (68.3)	22 (44.0)	.002
Severe/profound	59 (31.7)	28 (56.0)	
Ethnicity N (%)			
White	171 (91.9)	49 (98.0)	
Non-White	15 (8.1)	1 (2.0)	.13
APOE ε4 allele,[a] N (%)	32 (17.6)	13 (26.0)	.18
Risk score cut-point, N (%)	10 (1.8)	40 (80.0)	<.001

[a]Four people are missing *APOE* genotype.

TABLE 2 Demographic characteristics for participants without cognitive or functional decline and those with prevalent AD

Characteristics	Without cognitive/ functional decline	Prevalent AD	*p*
N	186	42	
Age (mean ± SD)	48.6 ± 6.7	57.7 ± 7.9	<.001
Gender, N (%)			
Male	44 (23.7)	15 (35.7)	.11
Female	142 (76.3)	27 (64.3)	
Level of intellectual disability, N (%)			
Mild/moderate	127 (68.3)	17 (40.5)	.001
Severe/profound	59 (31.7)	25 (59.5)	
Ethnicity, N(%)			
White	171 (91.9)	40	.46
Non-White	15 (8.1)	(95.2)	
APOE ε4 allele,[a] N (%)	32 (17.6)	12 (31.6)	.05
Risk score cut-point, N (%)	10 (1.8)	34 (81.0)	<.005

[a]Eight people are missing *APOE* genotype.

2.6 | Statistical analysis

Statistical analyses were conducted using the R (V 3.3.3) statistical software,[34] SPSS 24 (IBM), and SAS. Support vector machine (SVM) analyses were conducted to create proteomic profiles specific for prevalent (AD) dementia and prevalent MCI. SVM is primarily a classifier method that constructs hyperplanes in a multidimensional space that separates cases of different class labels. Diagnostic accuracy was assessed by receiver-operating characteristic (ROC) curves. Characteristics of participants who were without MCI or dementia at baseline and throughout the follow-up period (No cognitive/functional decline) and those with prevalent MCI or prevalent AD were compared using t tests and chi-square tests.

3 | RESULTS

From the initial cohort of 398 participants, a total of 186 participants were determined to be without MCI and dementia at baseline and throughout follow-up (No cognitive/functional decline); n = 50 were classified as having prevalent MCI at baseline and n = 42 were classified as having prevalent dementia and were included in this analysis. Table 1 presents the demographic characteristics of the participants with prevalent MCI compared with those without cognitive decline, and Table 2 presents the demographic characteristics of participants with prevalent AD compared with those without cognitive decline. Participants with MCI were older and more likely to have severe or profound levels of intellectual disability at baseline than participants who were without cognitive or functional decline at baseline or throughout follow-up. Participants with dementia were older, more likely to have severe or profound levels of intellectual disability, and more likely to carry an *APOE* E4 allele than participants who were without cognitive or functional decline at baseline or throughout follow-up.

First SVM was utilized to determine if our proteomic profile could detect prevalent MCI among adults with DS. With an optimized threshold cut-score of −0.987 from the SVM profile, the profile yielded an area under the curve (AUC) of 0.92, sensitivity (SN) = 0.80, and specificity (SP) = 0.98. The variable importance plot and ROC can be found in Figure 1. Next, analyses were run to determine if our proteomic profile could detect prevalent dementia. With an optimized SVM-based cut-score of −0.978, the AUC was 0.89, with a SN = 0.81 and SP = 0 .97. See Figure 2 for variable importance plots and ROC curve.

4 | DISCUSSION

These results strongly support the possibility of proteomic profiles having utility in detecting MCI and AD among adults with DS. In the current study, our full proteomic profile was highly accurate in detecting prevalent MCI (AUC = 0.92) and AD (AUC = 0.89) and in adults with DS. Detecting dementia among adults with DS is complicated by a range of factors, including severity of intellectual disability. The availability of a blood test that can be utilized to determine which adults with DS should undergo more comprehensive neurodiagnostic procedures can be of tremendous value to patients, caregivers, providers, and the medical system. As is the case with all initial screening tests, the overall goal is to develop tools that can be used by clinicians to identify individuals at risk of developing AD among adults with DS.[21] Specifically, the goal is to identify all of those patients who do not need more comprehensive, invasive, and costly medical testing. Therefore, a blood

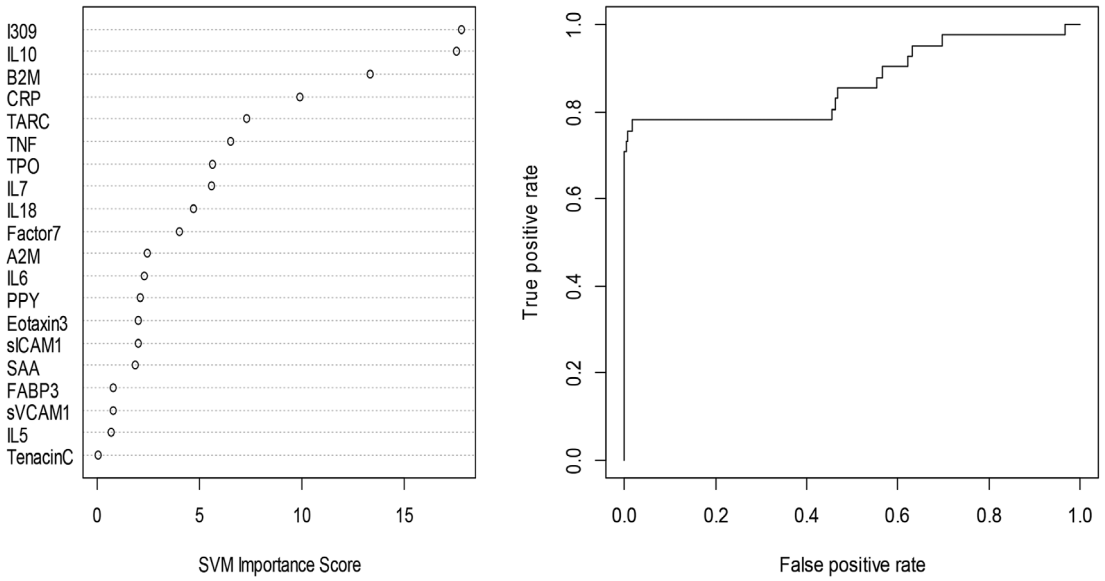

FIGURE 1 ROC plot and variable importance plot for proteomic profile discriminating MCI in adults with DS from healthy controls

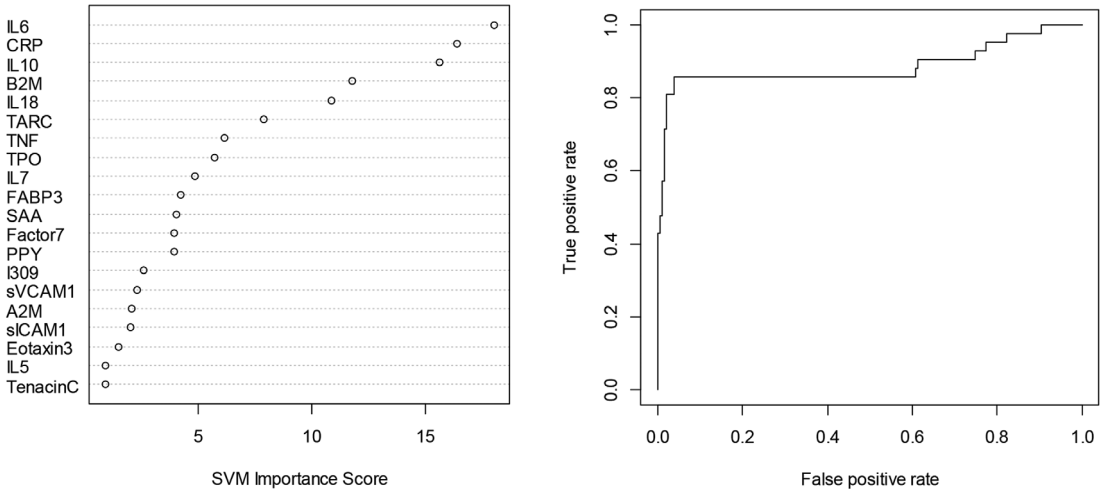

FIGURE 2 ROC plot and variable importance plot for proteomic profile discriminating AD in DS from healthy controls

test that can be implemented annually starting when the adult with DS is 30 years of age will benefit clinicians tremendously, as it will help inform if additional follow-up testing is necessary. By telling patients and family members that the individual does not appear to be exhibiting dementia at a particular time will greatly reduce family/caregiver stress, as well as reduce medical costs. When a positive finding arises on a blood screening test, the patient should be advised to undergo more costly and invasive testing. We have proposed this same multitiered approach for detecting AD in primary care settings, which can have a substantial impact on cost containment.[4] In addition, the availability of such a screening method can have substantial impact on novel clinical trial design. A blood-based screening tool has the potential to reduce overall cost and patient burden during the screening process, as well as increase availability of trial participation to a broader range of clinical populations including those with AD and DS.

Several research consortiums including the Alzheimer's Biomarker Consortium in Down syndrome (ABC-DS; https://www.nia.nih.gov/research/abc-ds), Down Alzheimer's Barcelona Neuroimaging Initiative, Horizon21 European Down Syndrome Consortium, and effort through the NIH INCLUDE initiative (https://www.nih.gov/include-project) have expanded on prior research efforts with the aim of identifying novel blood-based, neuroimaging, and genetic biomarkers underlying the transition from healthy normal aging to dementia in adults with DS. The goal of these consortiums is to better understand how such biomarkers can contribute to multiple potential pathways for targeted interventions. Such initiatives are helping to rapidly move toward advancement of precision-medicine approaches to novel clinical trials.

It is noteworthy that the proteomic algorithms derived from the current model for adults with DS and AD were heavily weighted toward

inflammatory markers for both MCI and AD, which is consistent with our prior work in AD in the general population.[20,21,35] In fact, we have identified a proinflammatory endophenotype derived from a reduced number of proteomic markers taken from the same AD proteomic profile examined in this study that identifies a specific subset of AD patients that appear to have benefited from a "failed" nonsteroidal anti-inflammatory drug (NSAID) trial.[36,37] Taking it one step further, the same set of proinflammatory endophenotypes may allow us to distinguish affected from unaffected adults with DS, which is consistent with the extant literature linking inflammation to DS.[38]

Prior work has shown that neuroinflammation is upregulated in fetal development in DS, which may exacerbate AD pathological development.[38] A recent meta-analysis[39] analyzing data across 19 studies (n = 957 patients diagnosed with DS and 541 healthy controls) found alterations in multiple inflammatory markers in DS. It is possible that our proinflammatory endophenotype will identify a specific subset of adults with DS for whom inflammation is a major driver of pathology and, therefore, anti-inflammatory interventions may be of particular use for this specific subgroup. This precision medicine approach has resulted in substantial strides in patient outcomes in cancer.[40,41] We are currently characterizing the proinflammatory endophenotype among this sample of adults with DS and will further that work with the ABC-DS collaborative effort.

Our results strongly support the utility of a blood-based profile for detecting MCI and AD risk among adults with DS. Future analyses are planned to examine the impact of including additional biomarkers previously linked to AD (ie, Aβ, tau, and NfL) along with the AD proteomic profile utilized in this study. The availability of a highly accurate proteomic profile for adults with DS would be of tremendous value to the field with regard to design of novel intervention trials, once validated. Because the cut-points were selected to provide the best discrimination between individuals with and without prevalent MCI or AD, it is important that these results be cross-validated in an independent sample. Cross-validation of this work will also address potential limitations in sample size that may have affected detection accuracy of the blood-based profiles. Future work should also expand to evaluate potential ethnic differences in the blood-based biomarker profiles as has been done in the broader AD population. These analyses (cross-sectional and longitudinal) are built into the ongoing Alzheimer's Biomarker Consortium—Down syndrome (ABD-DS) studies and will serve to provide an independent evaluation of our blood-based profile.

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