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Longitudinal Dynamics of the Blood Proteome Within the Alzheimer Spectrum in Down Syndrome

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Abstract

Background and Objectives

Adults with Down syndrome (DS) have an increased risk of developing early Alzheimer disease. While our previous cross-sectional study investigated the blood proteome in the context of Alzheimer in DS, identifying CBLN4, CD14, C-X-C motif chemokine 17 (CXCL17), ectodysplasin A2 receptor (EDA2R), glial fibrillary acidic protein (GFAP), insulin-like growth factor binding protein-2 (IGFBP2), neurofilament light (NFL), SEPTIN3, and SPON1 as proteins of interest, longitudinal trajectories remain mostly unexplored. We aimed to characterize the longitudinal dynamics of these plasma proteins to evaluate their potential contribution to disease pathophysiology and associated cognitive decline.

Methods

Adults with diagnosis of DS and ability to understand instructions of neuropsychological assessments were recruited at Ludwig Maximilians University Hospital Munich, returning for at least 1 annual follow-up visit for repeated clinical assessment, neuropsychological testing, and blood sample collection after baseline visit. Longitudinal blood protein dynamics were assessed using OLINK technology. Bayesian modeling analyzed longitudinal protein trajectories and their impact on cognitive performance. Spearman correlations of regression-derived rates of change investigated relationships between proteins and cognitive subdomains stratified by clinical diagnosis.

Results

We included 59 adults with DS (46% female, median age = 32 years [interquartile range: 27–47]). All completed the first annual follow-up visit (median duration 13.37 months [12.35–20.95]), with 14 of them returning for a follow-up 2 visit (median 25.43 months [24.79–33.8]). Stratified analysis included 13 individuals with DS with (38% female, 54 years [49–58]) and 41 without diagnosis of cognitive decline (49% female, 29 years [24–35]). Cluster of differentiation 14, CXCL17, EDA2R, GFAP, IGFBP2, NFL, SEPTIN3, and SPON1 exhibited longitudinal increase, while CBLN4 decreased (all posterior distributions ≥ 99.12%), with age. Protein baseline levels were associated with cognitive decline over time while controlling for age in the whole cohort (all posterior distributions ≥ 94.75%). After correction for multiple comparisons, no longitudinal changes in protein markers exhibited a significant relationship when correlated with changes in cognitive subdomain performance within subcohorts.

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Supplementary Material

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Glossary

95% CrI = credible interval; **AD** = Alzheimer disease; **aDS** = asymptomatic DS; **APP** = amyloid precursor protein; **CD14** = cluster of differentiation 14; **chr21** = chromosome 21; **CXCL17** = C-X-C motif chemokine 17; **DS** = Down syndrome; **DSAD** = Down syndrome–associated Alzheimer disease; **EDA2R** = ectodysplasin A2 receptor; **GFAP** = glial fibrillary acidic protein; **ID** = intellectual disability; **IGFBP2** = insulin-like growth factor binding protein-2; **LMU** = Ludwig Maximilians University; **LOO-CV** = leave-one-out cross-validation; **NFL** = neurofilament light; **PD** = probability of direction.

Discussion

In DS, longitudinal characterization of all previously identified proteins revealed distinct trajectories over time and an association of baseline levels with future cognitive decline. This suggests potential contributions of these proteins to the complex underlying pathophysiology of Alzheimer in DS and should motivate further investigation.

Introduction

The triplication of the amyloid precursor protein (APP) gene on chromosome 21 (chr21) results in a considerably higher risk for Alzheimer disease (AD) in individuals with Down syndrome (DS) and therefore poses one of the major health threats in adult age. As early as adolescence, amyloid (Aβ) plaque formation begins, followed by successive tau hyperphosphorylation and, finally, cognitive decline.[1]

However, there is growing evidence that the triplication of chr21 causes systemic proteomic dysregulation, beyond the amyloidogenic pathway mentioned above, that could drive Down syndrome (DSAD) pathology.[2] For 1, several gene products of chr21 are involved in processes such as inflammation, oxidative stress, and neurogenesis,[3,4] a number of which have been discussed as contributing factors in DSAD pathophysiology, especially in the context of neuroinflammation.[5] Further pathologic events, arguably independent of direct gene dosage effects of chr21 such as cerebrovascular pathology,[6] impaired cell metabolism or dysregulated pathways of the nerve growth factor,[7] ultimately hint at a complex interplay of several pathophysiologic processes within the proteomic landscape of DS, possibly shaping disease trajectory and contributing to variability in symptom onset and disease progression in DSAD.

In line with this, we recently conducted an exploratory investigation into the blood proteome of DS leveraging OLINK technology, where we identified several disregulated pathways regarding immune function and cell-to-cell signaling, the extracellular matrix, and metabolic processes, confirmed glial fibrillary acidic protein (GFAP) and neurofilament light (NFL) as blood markers for symptomatic DSAD, and identified 7 additional proteins of interest regarding their pathophysiologic role in DSAD.[8] Functionally, these relate to astrocytic activity (ectodysplasin A2 receptor [EDA2R], insulin-like growth factor binding protein-2 (IGFBP2), synaptic function (cerebellin 4 ([BLN4], neuronal-specific septin-3 [SEPTIN3]), inflammatory processes (C-X-C motif chemokine 17 [CXCL17], cluster of differentiation 14 [CD14]), and amyloid processing (spondin-1 [SPON1]), with none of them encoded on chr21.[8]

The current work intended to characterize the longitudinal trajectories of these identified proteins, particularly around the expected symptom onset within the spectrum of DSAD,[9] and to further examine their temporal relationship with cognitive decline. By improving our understanding of their pathophysiologic relevance, we ultimately aimed at evaluating their potential as blood biomarkers of DSAD onset and progression.

Methods

Participants and Clinical Workup

Adult individuals with DS were recruited through our ongoing observational cohort study "AD21" conducted at the outpatient clinic of Ludwig Maximilians University (LMU) hospital, Munich, Germany. AD21 enrolls adults with the diagnosis of DS and the ability for understanding instructions in a neuropsychological examination to investigate DSAD through annual assessments of clinical symptoms, performance on a neuropsychological test battery, and biomarkers of AD pathology. All participants included in this analysis completed at least 1 follow-up visit between December 2017 and July 2024.

Where possible, we conducted chromosome analysis to assess the accurate type of trisomy 21 (full, translocation, mosaicism). To stratify intellectual disability (ID), the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), criteria[10] were used, categorizing each individual's ID into mild, moderate, severe, or profound, based on their premorbid best-ever level of functioning, as obtained from interviews with caregivers, neuropsychological assessment, behavioral observations, and review of medical records. Individuals with severe or profound ID as their premorbid best-ever level were excluded from this analysis because of low completion rate in cognitive assessments.

Clinical diagnosis of dementia or mild cognitive impairment was reached independently by 2 neurologists referencing a predefined diagnostic algorithm[11] at baseline and was re-evaluated with each follow-up visit. For this, changes in behavior, cognition, and activities of daily living were assessed based on

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patient and caregiver information. Differential diagnoses were then excluded through neurologic examination and blood workup as well as an individual cognitive assessment performed by specifically trained neuropsychologists leveraging the validated German version of the Cambridge Cognitive Examination for Older Adults with Down Syndrome (CAMCOG-DS). The domains assessed included orientation, language, memory, attention, praxis, abstract thinking, and visual perception.[12]

A final evaluation of all examinations then either led to the diagnosis of symptomatic DS individuals, including only dementia and mild cognitive impairment in the context of AD (sDSAD) while excluding all remaining cases of cognitive decline because of a secondary cause or unclear etiology, or to the classification of asymptomatic DS (aDS), referring to individuals with DS with no signs of new impairments in cognition, behavior, or daily living activities.

For 5 individuals, diagnoses changed with follow-up: One participant converted to sDSAD, whereas 4 no longer met the criteria for sDSAD. All 5 were excluded from diagnosis-specific analyses to ensure homogeneity within each subcohort.

Where available, CSF biomarkers obtained during routine clinical diagnostics were used for A/T/N-classification.[13] These analyses were performed by an accredited external laboratory using commercially available immunoassays, with subsequent classification being based on the laboratory-provided cut-offs for amyloid-1–42/1–40 ratio (A-ratio, cut-off >5.5%; IBL Hamburg, RE59661 and RE59651), total tau (tTau, cut-off <445 pg/mL; AJ Roboscreen GmbH Leipzig, RE59631), and phospho-tau-181 (pTau181, cut-off <61 pg/mL; Fujirebio INNOTEST #81574).

Neuroimaging was acquired where possible as part of clinical workup. MRI included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences using the Siemens 3T Magnetom Prisma Scanner (Siemens, Erlangen, Germany). PET neuroimaging on a Siemens Biograph-64 system was acquired using 18F-florbetaben (295 MBq) 90–110 minutes postinjection. 18F-PI-2620-PET (185 MBq) was performed with dynamic emission recording (0–60 minutes after injection, 30–60-minute window for visual interpretation). For intensity scaling, cerebellar gray matter was referenced for all tracers. More details on patient workup can be found in the preceding publication.[8]

Owing to small samples sizes at baseline for CSF (n = 6) and imaging data (MRI: n = 10, 18F-florbetaben-PET: n = 5 18F-PI-2620-PET: n = 3), these variables were not included in statistical analysis.

Plasma Sample Collection and Analysis

With each visit, blood samples were collected into EDTA tubes from nonfasting participants, centrifuged at 2000 × g for 10 minutes to obtain plasma, further aliquoted into polypropylene tubes and then stored at −80°C within 30–45 minutes after the initial blood draw. Protein analysis was run on the OLINK Explore 3072 Panel (Uppsala, Sweden), a multiplex immunoassay platform assessing the concentration levels of approximately 3,000 proteins in the respective blood samples. To complement previously obtained cross-sectional data,[8] the second assay run primarily consisted of follow-up samples. To enable integrated analysis across both runs, bridging samples from the first run were included in the second, thereby permitting normalization and control for inter-run variation. For the current run, the intra-assay and interassay coefficient of variation for the proteins measured in each kit ranged from 7% CV to 15% CV, resulting in a median of 9% CV for both, which is an expected performance range for high-throughput proximity extension assay.[14] After quality control, the values of the final data set were transformed into an arbitrary unit of normalized protein expression (NPX, log2-transformed) ready for use in statistical analysis.

Statistical Analysis

All statistical analyses were performed on RStudio (version 2023.06.1 + 524).[15]

Baseline demographics were summarized as median with interquartile range for continuous variables and count percentage for categorical variables. Group comparisons were conducted using Mann-Whitney *U* tests for continuous and Fisher exact tests for categorical variables.

For more sophisticated analysis of longitudinal protein level dynamics and their association with markers of cognitive performance, Bayesian hierarchical models[16] were used leveraging brms.[17]

All models were run with 4 chains and 10,000 MCMC iterations, 5,000 of which were designated to warm up, and a thinning parameter of 10, leveraging 4 cores. Owing to differences in dimensions, all continuous variables were scaled before model run. Priors were specified as weakly informative after sensitivity analysis, thereby promoting certain regularization while allowing the data to inform the posterior. Specifically, variables were assigned N (0,1) priors, while the intercept was assigned a broader N (0,3) prior. For Gaussian likelihood models, an exponential (1) prior was used. For Student *t* models, a Student *t* (3, 0, 10) prior was assigned.

Model performance was evaluated by inspecting chain mixing, R hat value as a measure of convergence, sufficiency of bulk and tail estimated sample size, and pareto k. For the latter, persisting problematic observations for respective outcomes were addressed by increasing MCMC iterations to 11,000, resulting in improved posterior diagnostics.

Posterior summaries were reported as posterior mean estimate with corresponding posterior standard deviations and equal-tailed 95% credible intervals (95% CrIs), representing the estimated magnitude of effect and its associated uncertainty. An effect was considered strong when its 95% CrI excluded zero. For this, the probability of direction (PD) assessed the maximum proportion of an effect by quantifying

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its directional certainty away from 0, either in a positive or negative direction. As a measure of explained variance, we further assessed the corresponding R^2 value for each model.

For all models, baseline age was included as a fixed effect, if not already assigned as predictor, to allow for the longitudinal investigation of protein levels while controlling for aging effects. Further covariates such as sex and, in the case of a cognitive outcome, premorbid ID level were included where appropriate but only retained if they contributed meaningfully to model performance, as determined by leave-one-out cross-validation (LOO-CV). Similarly, the choice between Gaussian and Student t distributions was guided by LOO-CV, with the latter preferred in cases of heavier-tailed residuals. All longitudinal models included a random intercept and random slope for each individual to account for within-subject variability over time.

First, we investigated temporal changes in NPX levels along the age spectrum as well as over the time since baseline to learn more about the scale and longitudinal direction of each biomarker change in respect to the observed DS life span as well as the observed study period:

Model 1: NPX ~ age (+sex).

Model 2: NPX ~ months from baseline + baseline age (+sex).

Subsequently, we aimed at testing the effect of baseline NPX levels for their significance to longitudinal cognitive performance as measured by the CAMCOG-DS (in % as ratio of achieved score and achievable score):

Model 3: CAMCOG-DS% ~ months from baseline* baseline NPX + baseline age (+ premorbid ID) (+sex).

As a secondary exploratory analysis, we repeated the analysis of Model 2 and 3 while stratifying by subgroups to assess whether certain protein dynamics might be associated with clinical status:

Model 4: NPX ~ months from baseline*diagnosis + baseline age (+sex).

Model 5: CAMCOG-DS% ~ months from baseline*baseline NPX*diagnosis + baseline age (+ premorbid ID) (+sex).

Finally, to explore monotonic associations on subject level of rates of change between cognitive outcomes and NPX levels of all 9 proteins, individual slopes were obtained by ordinary least squares regression of each outcome over time. With this approach, we aimed to avoid hierarchical shrinkage and preserve natural between-subject variability for this rank-based association analysis. The obtained individual slopes were subsequently entered into a pairwise spearman correlations, conducted separately within the subgroups of sDSAD and aDS. After applying a correction for false discovery rate because of multiple comparisons, a p value below 0.05 was considered significant.

Standard Protocol Approvals, Registrations, and Participant Consents

All individuals were recruited from the outpatient clinic at LMU hospital Munich in Germany, where our study was approved by the LMU ethics committee (DS: #17–126) and is conducted in accordance with the Declaration of Helsinki. Each participant or their respective legal guardian provided informed written consent before study enrolment.

Data Availability

All raw data and scripts relevant to this article are available to researchers on reasonable request. Raw data will be shared once a data use agreement has been signed, after approval of a data request which should include a project rationale detailing hypotheses and proposed statistical analysis plan.

Results

Demographics

For this longitudinal analysis, samples of 59 adults with DS were included (Table 1). The subcohorts for diagnosis-stratified analysis revealed that sDSAD were significantly older than aDS, and, as expected, sDSAD also performed worse on the CAMCOG-DS. Meanwhile, there were no significant differences in distribution of sex or premorbid ID level. Finally, blood leucocyte levels as a parameter of systemic inflammation showed slightly higher levels in sDSAD while still within the clinically acceptable range.

Characterizing the Longitudinal Proteomic Trajectories in DS

Given that DSAD is considered a genetic form of AD where, similar to autosomal dominant AD, pathology accumulates with increasing age, thereby creating observable stages of disease progression, we first aimed to investigate the longitudinal dynamics of each protein along the age spectrum in DS (Model 1, Figure 1, for individual trajectories eFigure 1). With age as predictor, we found strong evidence for gradual decreases in NPX blood levels for CBLN4. Furthermore, there were longitudinal increases in NPX levels for all of the remaining proteins, namely CD14, CXCL17, EDA2R, GFAP, IGFBP2, NFL, SEPTIN3, and SPON1, across the investigated age span of adults with DS, as displayed in Table 2 and eTable 1.

Subsequently, we investigated whether longitudinal development of protein levels were different from initial baseline levels within DS while controlling for baseline age (Model 2), thereby assessing longitudinal trajectories beyond a potential age effect. Here, we found convincing evidence of rising proteins levels over time for CD14, CXCL17, EDA2R, and GFAP. Furthermore, there were subtle hints of increasing concentrations for NFL and SPON1, too; however, these corresponding CrI included zero, allowing for no definite estimation of the direction of effect with a PD of 91.95% and 96.05%, respectively. Finally, there were no relevant longitudinal changes present for IGFBP2, SEPTIN3, and CBLN4. Detailed results can be found in eTable 2.

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Table 1 Descriptive Baseline Demographic Information on All Cohorts Investigated in This Study

	Whole DS cohort	Subcohorts according to clinical status		
		aDS	sDSAD	
	N = 59	N = 41	N = 13	*p* Value
Age (y)	32 (27–47)	29 (24–35)	54 (49–58)	<0.001
Participants with follow-up, (%)				
Follow-up 1	59 (100)	41 (100)	13 (100)	
Follow-up 2	14 (24)	7 (17)	5 (38)	
Time from baseline (m)				
Follow-up 1	13.37 (12.35–20.95)	13.37 (12.38–22.12)	12.53 (11.15–13.62)	
Follow-up 2	25.43 (24.79–33.8)	25.47 (24.62–31.2)	25.4 (24.97–25.4)	
Sex, (%)				0.5
Female	27 (46)	20 (49)	5 (38)	
Male	32 (54)	21 (51)	8 (62)	
ID best level, (%)				0.2
Mild	36 (61)	28 (68)	6 (46%)	
Moderate	23 (39)	13 (32)	7 (54%)	
CAMCOG-DS (%)	60 (52–74)	67 (55–76)	57 (35–60)	0.017
NA	1	1	0	
A(myloid)				
Positive	7	0	6	
CSF	4		4	
Imaging	4		3	
Negative	3	3	0	
CSF	1	1		
Imaging	2	2		
NA	49	38	7	
T(au)				
Positive	3	0	3	
CSF	2		2	
Imaging	1		1	
Negative	3	1	1	
CSF	3	1	1	
Imaging	1			
NA	53	40	9	
N(eurodegeneration)				
Positive	5	0	5	
CSF	2		2	
Imaging	3		3	
Negative	10	8	0	

Continued

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Table 1 Descriptive Baseline Demographic Information on All Cohorts Investigated in This Study *(continued)*

	Whole DS cohort	Subcohorts according to clinical status		
		aDS	sDSAD	
	N = 59	N = 41	N = 13	*p* Value
CSF	2	1		
Imaging	8	7		
NA	44	33	8	
Leukocytes/uL	5.90 (4.80–6.80)	5.60 (4.70–6.40)	6.90 (6.00–7.50)	0.018
NA	8	5	2	
NPX levels at baseline				
CBLN4	0.36 (0.01 to 0.56)	0.45 (0.27 to 0.63)	−0.20 (−0.34 to 0.23)	8.9E-05
CD14	0.35 (0.05 to 0.60)	0.22 (0.00 to 0.52)	0.71 (0.48 to 0.88)	9.9E-05
CXCL17	1.37 (0.98 to 1.86)	1.21 (0.89 to 1.47)	2.11 (1.88 to 2.49)	1.7E-07
EDA2R	0.50 (0.27 to 0.86)	0.42 (0.13 to 0.52)	1.18 (0.92 to 1.45)	4.8E-09
GFAP	0.33 (−0.10 to 1.34)	0.11 (−0.26 to 0.45)	2.04 (1.82 to 2.44)	2.2E-09
IGFBP2	0.25 (−0.40 to 0.86)	0.06 (−0.72 to 0.35)	0.96 (0.62 to 1.13)	2.1E-05
NFL	0.64 (0.15 to 1.37)	0.44 (−0.06 to 0.68)	2.13 (1.37 to 2.85)	2.8E-09
SEPTIN3	1.12 (0.59 to 1.68)	0.98 (0.42 to 1.38)	1.83 (1.41 to 2.23)	0.00222
SPON1	0.33 (0.08 to 0.61)	0.22 (0.05 to 0.37)	0.73 (0.52 to 0.87)	9.3E-07

Abbreviations: aDS = asymptomatic Down syndrome; CAMCOG-DS = Cambridge Cognitive Examination for Older Adults with Down Syndrome; CBLN4 = cerebellin 4; CD14 = cluster of differentiation 14; CI = credible interval; CXCL17 = C-X-C motif chemokine 17; EDA2R = ectodysplasin A2 receptor; GFAP = glial fibrillary acidic protein; ID = intellectual disability; IGFBP2 = insulin-like growth factor binding protein-2; NA = not available; NFL = neurofilament light chain; NPX = OLINK-provided normalized protein concentration; sDSAD = symptomatic Down syndrome; SEPTIN3 = neuronal-specific septin-3; SPON1 = spondin-1.

Effect of Baseline Protein Levels on the Rate of Change in Cognitive Performance in DS

Having investigated the temporal characteristics of these proteins, we then aimed to evaluate whether their baseline NPX levels would be associated with longitudinal changes in cognition in DS depicted in Figure 2 as well as Table 3 and eTable 3, therefore suggesting these proteins might have clinical relevance as correlates of DSAD progression. While most sDSAD individuals demonstrated declining cognitive performance over time, a small number showed stable or slightly improved scores, consistent with intraindividual variability and practice effects in repeated neuropsychological assessments.[12]

For the intended analysis, we fitted models with the CAMCOG-DS overall performance score as outcome while accounting for baseline age (Model 3). Here, we identified several proteins whose baseline levels were associated with accelerated cognitive decline in the DS cohort.

Specifically, higher baseline NPX levels of CD14, CXCL17, EDA2R, GFAP, IGFBP2, NFL, and SPON1 were associated with worse performance on the CAMCOG-DS over time. Again, SEPTIN3 showed a tendency with a PD of 94.75, but a credible interval marginally including zero, overall suggesting that DS individuals with higher baseline levels of these proteins might also experience faster cognitive decline. Conversely, CBLN4 was positively associated with cognitive change, indicating that higher baseline levels may be associated with slower decline or more stable performance over time.

Stratified Analysis According to Clinical Status

To assess whether these changes were driven by one of the diagnostic groups, we conducted a subgroup analysis stratified by clinical diagnosis of either sDSAD or aDS (Model 4 and 5).

First, we repeated the analysis of Model 2, with the interaction term of time since baseline and clinical diagnosis as predictor (Model 4). For all 9 proteins, there was no strong evidence for group-specific differences in proteomic trajectories over the observed time of follow-up as reported in eTable 4 and eFigure 2. Accordingly, estimates for this interaction were rather small in magnitude, ranging from −0.07 to 0.09, with substantial uncertainty, represented by wide CrI spanning zero and limited directional consistency as assessed by PD. Notably, SEPTIN3 included zero only marginally in its CI, with the PD indicating most of the posterior distribution located below zero, suggesting a possible higher rate of decline in sDSAD compared with aDS (−0.07 [−0.16, 0.02], PD = 93%).

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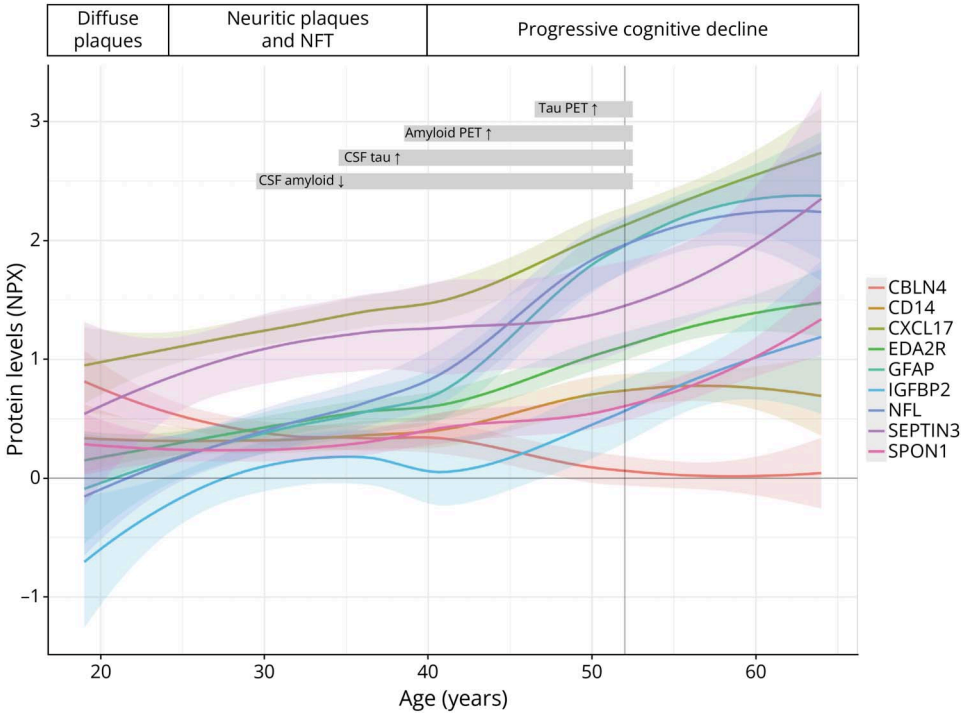
Figure 1 Longitudinal Protein Levels (NPX) Across the DS Spectrum as Approximated by Individual LOESS-Curves of Each of the Protein's Data Points



The gray vertical line indicates the approximate expected age of clinical dementia symptom onset, the horizontal banners the expected time point of respective biomarker changes, all derived from Fortea et al.[9] CBLN4 = cerebellin 4; CD14 = cluster of differentiation 14; CXCL17 = C-X-C motif chemokine 17; DS = Down syndrome; EDA2R = ectodysplasin A2 receptor; GFAP = glial fibrillary acidic protein; IGFBP2 = insulin-like growth factor binding protein-2; LOESS = Locally Estimated Scatterplot Smoothing; NFL = neurofilament light chain; NFT = neurofibrillary tangles, NPX = OLINK-provided normalized protein concentration; SEPTIN3 = neuronal-specific septin-3; SPON1 = spondin-1.

Second, we repeated the analysis of Model 3 with an additional interaction term to see whether the association of baseline NPX levels on longitudinal cognitive performance would differ by clinical diagnosis (Model 5). Here, IGFBP2 demonstrated a statistically credible interaction effect (−0.22 [−0.43, −0.02], PD = 98.46%), suggesting that elevated baseline levels are associated with an accelerated rate of cognitive decline in sDSAD vs aDS.

Table 2 Model Output for the Longitudinal Development of NPX Levels Along the Age Spectrum in DS

	Estimate	Lower-95% CI	Upper-95% CI	PD, (%)	R^2
CBLN4	−0.47	−0.67	−0.26	100	0.693
CD14	0.4	0.19	0.61	100	0.600
CXCL17	0.74	0.58	0.91	100	0.869
EDA2R	0.79	0.64	0.95	100	0.872
GFAP	0.84	0.68	1.01	100	0.928
IGFBP2	0.42	0.21	0.65	100	0.853
NFL	0.76	0.6	0.92	100	0.883
SEPTIN3	0.28	0.05	0.52	99.12	0.976
SPON1	0.52	0.32	0.72	100	0.746

Abbreviations: CBLN4 = cerebellin 4; CD14 = cluster of differentiation 14; CI = credible interval; CXCL17 = C-X-C motif chemokine 17; DS = Down syndrome; EDA2R = ectodysplasin A2 receptor; GFAP = glial fibrillary acidic protein; IGFBP2 = insulin-like growth factor binding protein-2; NFL = neurofilament light chain; NPX = normalized protein expression; PD = probability distribution; R^2 = R-squared representing the proportion of variance explained by the model; SEPTIN3 = neuronal-specific septin-3; SPON1 = spondin-1.

CBLN4, GFAP, NFL, and SPON1 also showed moderately high probabilities of a negative interaction effect (PD = 89.46%–95.58%), though their CrI slightly overlapped zero, indicating some uncertainty in the direction of the effect, despite posterior distributions being largely skewed toward a negative estimate. The remaining protein NPX baseline levels showed no meaningful interaction effects, with wide intervals spanning zero and low PD values, providing little evidence for a diagnosis-specific longitudinal association with changes in CAMCOG-DS performance over time, as displayed in eTable 5.

Correlations of Protein Trajectories With Changes in Subdomains of Cognitive Performance

Finally, we examined the relationship between the proteomic rates of change with each other as well as cognitive performances on subdomains as assessed by CAMCOG-DS, while stratifying by diagnostic group, reported in eTable 6 and 7 and visualized in eFigure 3. After controlling for multiple comparisons, we observed several weak to moderate correlations between CBLN4 and EDA2R ($r = 0.73$, $p < 0.001$), IGFBP2 ($r = 0.49$, $p = 0.039$), and SPON1 ($r = 0.67$, $p < 0.001$), as well as between EDA2R and IGFBP2 ($r = 0.61$, $p = 0.002$). Meanwhile, no rate of change correlation survived

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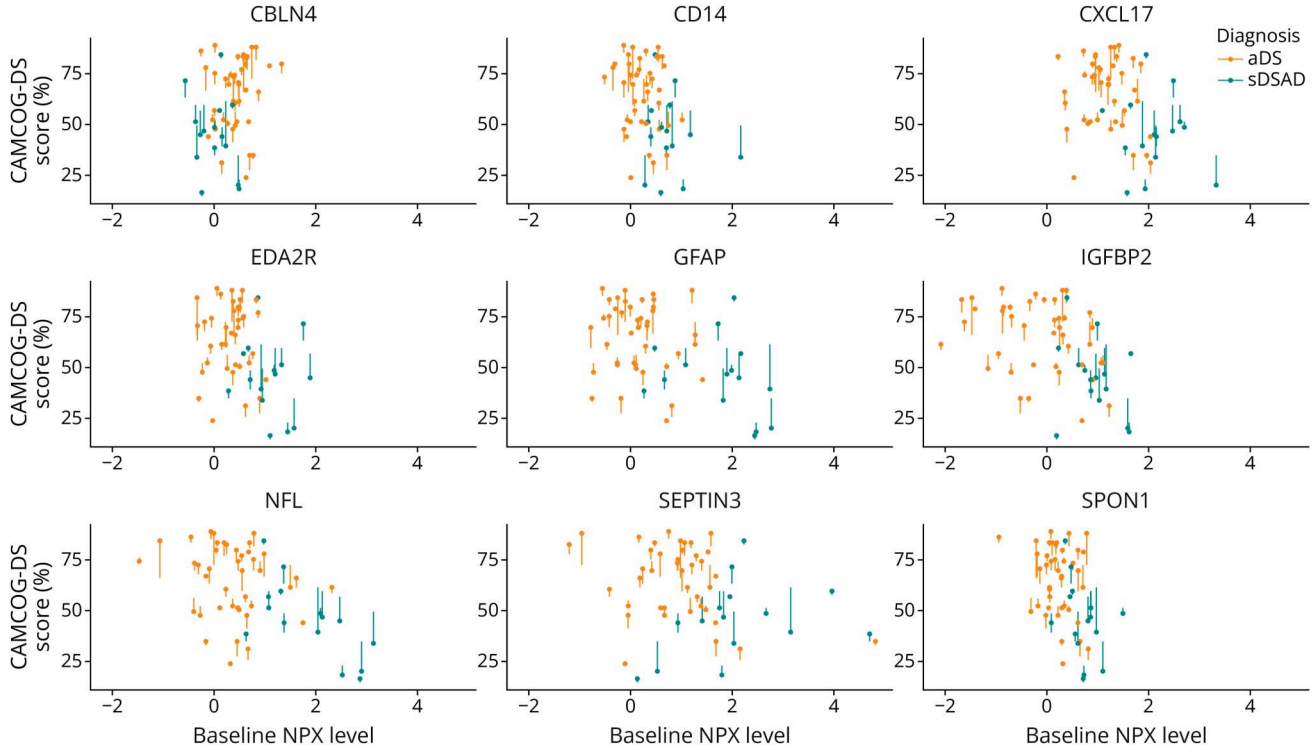
Figure 2 Visualization of Individual Trajectories in Repeated Assessments of Cognitive Performance Over Time, According to Baseline NPX Levels



For each individual, at least 2 CAMCOG performances are displayed and connected with a line to display the longitudinal development of cognitive score relative to NPX values, with the dot indicating the latest cognitive performance score per individual. aDS = asymptomatic DS; CAMCOG = Cambridge Cognitive Examination for Older Adults; CBLN4 = cerebellin 4; CD14 = cluster of differentiation 14; CXCL17 = C-X-C motif chemokine 17; EDA2R = ectodysplasin A2 receptor; GFAP = glial fibrillary acidic protein; IGFBP2 = insulin-like growth factor binding protein-2; NFL = neurofilament light chain; NPX = OLINK-provided normalized protein concentration; sDSAD = symptomatic DS individuals, including only dementia and mild cognitive impairment in the context of AD; SEPTIN3 = neuronal-specific septin-3; SPON1 = spondin-1.

FDR-correction in sDSAD and neither group retained significant relationships for longitudinal protein dynamics and cognitive changes over time after FDR correction.

Discussion

In this longitudinal analysis, we further characterized 9 previously identified plasma proteins in the context of DSAD.[8] Longitudinally, plasma NPX levels of all proteins increased, except for CBLN4 which decreased, along age in DS. Furthermore, plasma levels for CD14, CXCL17, EDA2R, GFAP, and IGFBP2 increased during the time of follow-up, while stratified analysis revealed no differences for aDS vs sDSAD over time. Baseline NPX levels were associated with future cognitive decline in DS, but only IGFBP2 exhibited a distinct trajectory when considering aDS vs sDSAD. Rate-of-change correlations in the stratified subcohorts revealed several positive protein-protein in aDS but not sDSAD. This lack of group-specific findings within our longitudinal window might be due to short follow-up durations and small sample sizes because significant longitudinal differences between DSAD and healthy DS in blood have been described for NFL and GFAP.[18]

Baseline NPX levels of all proteins were associated with cognitive decline over time while controlling for age, suggesting that initial plasma levels may represent biological processes relevant for later cognitive deterioration in the context of DSAD that are not solely explained by chronological age itself.

For IGFBP2, we found a steeper cognitive decline with higher baseline levels for sDSAD compared with aDS, suggesting that its baseline burden may be particularly informative before clinical symptoms eventually emerge. So far, few of the proteins investigated have been linked to disease progression or cognitive outcomes in DSAD. However, baseline plasma levels of NFL and GFAP have indeed been reported to predict future cognitive decline and dementia progression in DS.[19] Characterizations of the other proteins have predominantly been performed in the euploid population or animal models, where CBLN4 was reported as part of a plasma protein set able predict future risk of dementia,[20] and higher plasma levels of IGFBP2 have been related to higher conversion rates to AD.[21] Meanwhile, increased SPON1 expression in mice resulted in improved cognition while reducing amyloid load.[22] Furthermore, higher plasma levels of CD14 were linked to greater decline in executive function,[23] and CXCL17 as well as

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Table 3 Estimated Effect of Baseline NPX Levels of Each Protein on Overall Longitudinal Cognitive Performance Since Baseline

	Estimate	Lower 95% CI	Upper 95% CI	PD, (%)	R^2
CBLN4	0.06	0	0.12	97.35	0.949
CD14	−0.09	−0.14	−0.04	100	0.950
CXCL17	−0.1	−0.16	−0.04	99.95	0.951
EDA2R	−0.09	−0.15	−0.03	99.85	0.951
GFAP	−0.12	−0.17	−0.06	100	0.950
IGFBP2	−0.09	−0.14	−0.04	99.95	0.948
NFL	−0.12	−0.18	−0.07	100	0.952
SEPTIN3	−0.05	−0.11	0.01	94.75	0.945
SPON1	−0.09	−0.15	−0.03	99.65	0.947

Abbreviations: CBLN4 = cerebellin 4; CD14 = cluster of differentiation 14; CI = credible interval; CXCL17 = C-X-C motif chemokine 17; DS = Down syndrome; EDA2R = ectodysplasin A2 receptor; GFAP = glial fibrillary acidic protein; IGFBP2 = insulin-like growth factor binding protein-2; LOO-CV = leave-one-out cross-validation; NFL = neurofilament light chain; NPX = normalized protein expression; PD = probability distribution; R^2 = R-squared representing the proportion of variance explained by the model; SEPTIN3 = neuronal-specific septin-3; SPON1 = spondin-1.
The model further accounted for baseline age and ID level, as well as sex if improving the model as assessed by LOO-CV.

EDA2R have recently been identified as a relevant plasma marker for predicting AD,[24] while EDA2R was also associated with cognitive performance.[25] Taken together, our findings suggest that baseline levels of the investigated set of proteins, reflecting multiple, pathophysiologic processes such as neurodegeneration, synaptic integrity, amyloid processing, growth factor regulation, and immune activity, may associate with later cognitive decline across the DSAD spectrum. Beyond the singular amyloid pathway, these proteins might therefore mirror complementary aspects of the underlying DSAD pathophysiology that precedes clinically relevant cognitive decline. However, given the limited duration of follow-up and sample size, these findings should not be interpreted as evidence of a causal role of these proteins for progressive cognitive decline, larger studies with longer observation periods are needed to further explore their association with longitudinal cognitive changes in DSAD.

By contrast, rate of change correlations between proteins and cognitive performance on the CAMCOG-DS as a whole as well as its subdomains revealed no significant relationships after correction for multiple comparison. This could be due to our small sample size, where variability across individuals, especially when investigating rates of change in an exploratory setting, might influence findings. Replication in larger cohorts with longer follow-up durations will be important to investigate potentially meaningful biological relationships of each protein with CAMCOG-DS subdomains.

Given that our analysis found that all proteins levels increased longitudinally with chronological age, while some protein levels also rose over time from baseline while adjusting for age, an important consideration for the interpretation of our current findings is the role of potential age-related biological processes independent of DSAD pathology.

In DS, chronological age is however intrinsically linked to the development and progression of AD pathology because of the underlying triplication of APP on chr21, so much so, that it is by now considered a genetically determined form of AD.[26] The resulting, predictable cascade of biomarker and clinical changes is similar to what we see in autosomal dominant AD,[27,28] where chronological age can function both as a reference of disease stage and as a covariate that should be considered when examining biomarker associations. Therefore, aging-related and disease-related processes cannot be regarded as fully independent pathophysiologic dimensions within observational cohorts such as ours. While this limits the extent to which effects of age and disease can be disentangled, this constellation reflects a fundamental characteristic of disease trajectories in genetically determined diseases overall, rather than a unique limitation to our study.

Arguably, the partial overlap between age and time-since-baseline effects in this analysis suggests certain distinctions in temporal dimensions: While longitudinal increases along age likely represent a cumulative development of each protein along the spectrum of DSAD, the investigation into biomarker changes from baseline aims at capturing the observational window of the study while controlling for age within the model. Considering the rather short follow-up duration and small sample size, our findings might highlight proteins with more rapid trajectories, while the rest of the set could only be captured across the decades of disease development represented in our cohort.

While our analyses did not investigate proteomic mechanisms directly, studies suggest their involvement in pathways related to several biological pathways potentially relevant to the spectrum of DSAD pathophysiology.

CBLN4, SEPTIN3, and IGFBP2 have previously been associated with synaptic function and neuronal plasticity, with prior studies indicating potential roles in synaptic signaling and structural integrity,[29-31] coinciding with altered CSF levels in AD[21,32] and increased expression in AD neocortical tissue.[33] In the present cohort, higher baseline levels were associated with future cognitive decline, suggesting that these proteins may track neurobiological processes accompanying progressive dysfunction.

Furthermore, SPON1 and EDA2R seem to be involved in regulation of the extracellular matrix and cellular stress, having been linked to beta-secretase–related processing, apoptosis pathways, and inflammatory signaling,[34,35] as well as identified as features of AD.[36-38] The observed age-related increases and associations with cognitive decline may therefore reflect remodeling processes accompanying neurodegeneration.

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Finally, the inflammatory markers CD14 and CXCL17 also increased with age and were associated with cognitive decline. Both proteins partake in immune regulation and inflammatory signaling.[39,40] Given the general dysregulation of the immune system in DS, this is not surprising; however, CD14 plasma levels have been reported to rise in AD.[41] Therefore, they could also play a role in propagating neuroinflammatory processes within the context of DSAD.

While future work will be required to determine how these pathways interact and whether these markers reflect distinct mechanisms contributing to the pathophysiology of DSAD, our findings contribute to the existing evidence that these proteins may capture aspects of the biological processes underlying AD progression.

We acknowledge several limitations. First, our current sample size is rather small and the median follow-up time relatively short, potentially not fully capturing longitudinal trajectories. Second, diagnosis was predominantly based on clinical and neuropsychological assessments, with only few individuals providing further assessments supporting pathology markers of the ATN framework. This yields the risk of misclassification especially in early stages and guided our decision to exclude participants with changes in classification on follow-up from diagnosis-stratified longitudinal analyses. Accordingly, we were also unable to relate protein dynamics to direct measures of amyloid or tau pathology and relied mostly on clinical diagnosis. Future studies in larger samples, ideally incorporating biomarkers of AD pathology, will be important to further evaluate the relevance of these proteins and clarify their role in the pathophysiology of DSAD. Our current work should be considered within its context of a clinically defined disease trajectory. Finally, despite implementing bridging controls and normalization, residual assay-related variability may contribute some noise to the obtained data. Such batch effects pose an inherent challenge within the field of high-throughput proteomics, although evidence suggests that these are generally expected to be small.[14]

This work demonstrates that all 9 previously identified proteins rise or decrease, respectively, with age in our DS cohort, with results also suggesting an association between protein baseline levels and future cognitive change when controlling for age. Overall, this could suggest a potential involvement in the complex processes underlying DSAD. Further investigations into their role are needed to inform our current understanding of DSAD pathophysiology and, down the road, potentially generate novel insights into disease-modifying strategies.

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Author Contributions

O. Wagemann: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. G.S. Nuebling: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. K. Sandkühler: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Wlasich: major role in the acquisition of data. S.V. Loosli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Prix: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.C. Stockbauer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Marth: drafting/revision of the manuscript for content, including medical writing for content. A. Forte: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Vöglein: drafting/revision of the manuscript for content, including medical writing for content. S. Katzdobler: drafting/revision of the manuscript for content, including medical writing for content. A.M. Bernhardt: drafting/revision of the manuscript for content, including medical writing for content. F.J Martinez-Murcia: drafting/revision of the manuscript for content, including medical writing for content. C. Jiménez-Mesa: drafting/revision of the manuscript for content, including medical writing for content. G.U. Höglinger: drafting/revision of the manuscript for content, including medical writing for content. J. Levin: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

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Disclosure

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