Serum glial fibrillary acidic protein is a marker of disease severity in frontotemporal lobar degeneration

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Abstract

Objective: To assess the diagnostic and prognostic value of serum glial fibrillary acidic protein (GFAP) in a large cohort of patients with frontotemporal lobar degeneration (FTLD).

Methods: In this retrospective study, performed on 406 participants, we measured serum GFAP concentration with an ultrasensitive Single molecule array (Simoa) method in FTLD, Alzheimer’s disease (AD) and healthy ageing. We assessed the role of GFAP as marker of disease severity by analysing the correlation with clinical variables, neurophysiological data and cross-sectional brain imaging. Moreover, we evaluated the role of serum GFAP as a prognostic marker of disease survival.

Results: We observed significantly higher levels of serum GFAP in patients with FTLD syndromes, except progressive supranuclear palsy (PSP), compared with healthy controls, but not compared with AD patients. In FTLD, serum GFAP levels correlated with measures of cognitive dysfunction and disease severity, and were associated with indirect measures of GABAergic deficit. Serum GFAP concentration was not a significant predictor of survival.

Conclusions: Serum GFAP is a marker of disease severity in FTLD.
Introduction

Frontotemporal dementia (FTD) is a genetically and pathologically heterogeneous disorder characterized by personality changes, language deficits, and impairment of executive functions associated with the degeneration of frontal and temporal lobes. Different phenotypes have been defined on the basis of presenting clinical symptoms, i.e., the behavioural variant of FTD (bvFTD), the agrammatic variant of primary progressive aphasia (avPPA), and the semantic variant of PPA (svPPA) (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). A significant percentage of patients have associated extrapyramidal symptoms, as in progressive supranuclear palsy (PSP) (Höglinger et al., 2017) and corticobasal syndrome (CBS) (Armstrong et al., 2013).

These clinical phenotypes share common underlying molecular and pathological substrates, and in most cases, inclusions of microtubule-associated protein tau or TAR DNA-binding protein 43 (TDP-43) represent the pathological hallmarks of the disease (Cairns et al., 2007; Mackenzie et al., 2006).

The heterogeneity of clinical presentations, along with unpredictable neuropathology, has consistently precluded a straightforward staging of the disease. Considering the increasing development of disease-modifying therapies in the spectrum of frontotemporal lobar degeneration (FTLD), the demand for objective, easily accessible and low-cost biomarkers to evaluate disease severity and progression has significantly increased in the last years.

A multitude of markers of disease severity have been recognized in the last decade, ranging from neuroimaging with magnetic resonance imaging (MRI) or positron emission tomography (PET), to cerebrospinal fluid (CSF) biomarkers (Borroni et al., 2018). However, the use of imaging markers is prevented by the lack of common patterns across FTLD subtypes, and the helpfulness of CSF is limited by the sampling method that sometimes is regarded invasive.

Along with recently proposed neurophysiological markers, measuring FTLD-related neurotransmitter deficits non-invasively by transcranial magnetic stimulation (TMS) (Benussi et al., 2020c), a giant step forward towards potentially useful biomarkers has been made with the new
ultrasensitive Single molecule array (Simoa) approach and the discovery of potentially useful blood-based biomarkers. It has been clearly proven that concentrations of blood NfL, a marker of axonal damage, are increased in FTLD and may be related to parameters of disease severity and prognosis (Foiani et al., 2018; Meeter et al., 2016; Rohrer et al., 2016).

Moreover, recent studies have reported increased levels of glial fibrillary acidic protein (GFAP), which is a marker of astrogliosis secondary to neuronal damage, in several neurodegenerative disorders, including dementia with Lewy bodies, Alzheimer’s disease (AD) and both sporadic and genetic FTD (Abu-Rumeileh et al., 2019; Heller et al., 2020; Ishiki et al., 2016; Oeckl et al., 2019b, 2019a; Sudre et al., 2019). However, it has yet to be established if GFAP blood-based assays are reliable in all FTLD subgroups, including CBS and PSP, and if these correlate with disease severity and survival.

This retrospective study aimed at confirming and extending previous literature data, comprehensively assessing the clinical value of serum GFAP in a large cohort of FTLD patients.
Materials and Methods

Subjects

This retrospective study included 406 participants from two independent cohorts, 298 from the Centre for Neurodegenerative Disorders, University of Brescia, Italy and 108 from the IRCCS Istituto San Giovanni di Dio Fatebenefratelli, Brescia, Italy. The cohort consisted of 282 patients meeting probable clinical criteria for a syndrome in the FTLD spectrum, namely 130 bvFTD, 48 avPPA, 24 svPPA, 50 CBS and 30 PSP (Armstrong et al., 2013; Gorno-Tempini et al., 2011; Höglinger et al., 2017; Rascovsky et al., 2011). Moreover, 63 patients fulfilling clinical criteria for AD (McKhann et al., 2011) and 61 healthy controls (HC), recruited among spouses or caregivers, were included as well.

Each FTLD patient underwent a neurological evaluation, routine laboratory examination and a neuropsychological and behavioural assessment. In all cases, the diagnosis was supported by brain structural imaging, while CSF concentrations of T-tau, P-tau\textsubscript{181} and A\textbeta\textsubscript{1-42} were measured in a subset of cases (45.0%), to rule out AD, as previously reported (Borroni et al., 2014). Furthermore, in familial cases (based on the presence of at least one dementia case among first-degree relatives) and early onset sporadic cases, genetic screening for GRN, C9orf72 and MAPT P301L mutations was performed; given the low frequency of MAPT mutations in Italy (Fostinelli et al., 2018) we considered only the P301L mutation and we sequenced the entire MAPT gene only in selected cases.

Each participant underwent blood collection for measurements of serum GFAP, and a subset of FTLD patients underwent standardized brain Magnetic Resonance Imaging (MRI) at baseline on the same scanner (n=45) to evaluate the correlation between serum biomarkers and imaging data. Moreover, a subgroup of patients underwent TMS protocols (n=110) to assess the correlation between serum biomarkers and neurophysiological data. For the purpose of the present study, we considered TMS measures that partially and indirectly reflect the activity of several neurotransmitters, including GABA\textsubscript{A} by short interval intracortical inhibition (SICI), glutamate by...
intracortical facilitation (ICF), GABA\textsubscript{B} by long interval intracortical inhibition (LICI), and acetylcholine by short latency afferent inhibition (SAI) (Rossini et al., 2015; Ziemann et al., 2015).

Full written informed consent was obtained from all subjects according to the Declaration of Helsinki. The Brescia Ethics Committee approved the study protocol.

**Clinical evaluation**

At baseline patients underwent a standardized neuropsychological battery which included the mini-mental state examination (MMSE), the short story recall test, the Rey complex figure (copy and recall), phonemic and semantic fluencies, the token test, the clock-drawing test, and trail-making test (part A and part B). Disease severity was assessed with the FTLD modified clinical dementia rating (FTLD-modified CDR) sum of boxes scale, while the level of functional independence was assessed with the basic activities of daily living (BADL) and the instrumental activities of daily living (IADL) questionnaires. Furthermore, neuropsychiatric and behavioural disturbances were evaluated with the frontal behaviour inventory (FBI).

HCs underwent a brief standardized neuropsychological assessment (MMSE ≥27/30); psychiatric or other neurological illnesses were considered exclusion criteria.

**Serum GFAP**

Serum was collected by venipuncture, processed and stored in aliquots at -80°C according to standardised procedures. Serum GFAP was measured using a commercial…. The lower limits of detection for serum GFAP were 0.xxx pg/mL. Measurements were carried using an HD-X analyser (Quanterix, Billerica, MA) at the same study site on consecutive days, using the same batch of reagents, and the operators were blinded to all clinical information. Quality control samples had a mean intra-assay and inter-assay coefficient of variation of less than 8% and 20% respectively.
MRI acquisition, processing and analysis

Brain images were collected using 3 Tesla scanner (Siemens Skyra, Erlangen, Germany) equipped with a circularly polarized transmit-receive coil to obtain 3D magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted scans. Sequences were acquired with the following parameters:
- repetition time 2000 ms, echo time 2.92 ms, inversion time 850 ms, slice thickness 1.1 mm, voxel size 1.1×1.1×1.1, field of view 282 mm, flip angle 8°.

T1 scans were visually inspected and excluded from subsequent analyses if excessive motion blurring or artefacts were present. Then, images were processed and analysed with the Statistical Parametric Mapping software package (SPM12 v. 7771, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), running on MATLAB 9.2 (The MathWorks, Inc, Natick, MA USA). Images were spatially normalized to a reference stereotactic template (Montreal Neurological Institute, MNI), and smoothed by a Gaussian kernel of 10×10×10 mm full width at half maximum (FWHM). Grey matter was assessed by Voxel Based Morphometry (VBM) analysis (Premi et al., 2016)

Moreover, we considered white matter hyperintensities burden, computed on T1-weighted and T2 FLAIR images using the Wisconsin White Matter Hyperintensities Segmentation Toolbox version 1.3 (Ithapu et al., 2014). A per-subject summary measure of total white matter hyperintensities volume burden was automatically calculated on the probability map outputs, adjusting for intracranial volume to account for the differences in brain sizes (Paternicò et al., 2016).

The association between grey matter or white matter hyperintensities and serum GFAP values was considered. Age, gender and clinical phenotype were considered as confounding factors in both analyses. The statistical threshold was set at 0.05 and corrected for multiple comparisons using false discovery rate (FDR) at whole-brain level.

Transcranial Magnetic Stimulation
A TMS figure-of-eight coil (each loop diameter 70 mm – D702 coil) connected to a monophasic Magstim Bistim2 system (Magstim Company, Oxford, UK) was employed for all TMS paradigms, as previously reported (Benussi et al., 2019b). Electromyographic (EMG) recordings were performed from the first dorsal interosseous muscle using 9 mm diameter, Ag-AgCl surface-cup electrodes. The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified and filtered at 20 Hz and 2 kHz with a sampling rate of 5 kHz.

Resting motor threshold (RMT) was determined on the left motor cortex as the minimum intensity of the stimulator required to elicit motor evoked potentials (MEPs) with a 50 μV amplitude in 50% of 10 consecutive trails, recorded during full muscle relaxation.

SICI-ICF, LICI and SAI were studied using a paired-pulse technique, employing a conditioning-test design. For all paradigms, the test stimulus (TS) was adjusted to evoke a MEP of approximately 1 mV amplitude. For SICI and ICF, the conditioning stimulus (CS) was adjusted at 70% of the RMT, employing multiple interstimulus intervals (ISIs), including 1, 2, 3 ms for SICI and 7, 10, 15 ms for ICF (Kujirai et al., 1993; Ziemann et al., 1996). LICI was investigated by implementing two supra-threshold stimuli, with the CS adjusted at 130% of the RMT, employing ISIs of 50, 100 and 150 ms (Valls-Solé et al., 1992). SAI was evaluated employing a CS of single pulses (200 μs) of electrical stimulation delivered to right median nerve at the wrist, using a bipolar electrode with the cathode positioned proximally, at an intensity sufficient to evoke a visible twitch of the thenar muscles (Tokimura et al., 2000). Different ISIs were implemented (0, +4), which were fixed relative to the N20 component latency of the somatosensory evoked potential of the median nerve.

For each ISI and for each protocol, ten different paired CS-TS stimuli and fourteen control TS stimuli were delivered in all participants in a pseudo-randomized sequence, with an inter trial interval of 5 secs (±10%).
The conditioned MEP amplitude, evoked after delivering a paired CS-TS stimulus, was expressed as percentage of the average control MEP amplitude. Average values for SICI (1, 2, 3 ms ISI), ICF (7, 10, 15 ms ISI), LICI (50, 100, 150 ms ISI) and SAI (0, +4 ms ISI) were used for analysis. Stimulation protocols were conducted in a randomized order. Audio-visual feedback was provided to ensure muscle relaxation during the entire experiment and trials were discarded if EMG activity exceeded 100 μV in the 250 ms prior to TMS stimulus delivery. Less than 5% of trials were discarded for each protocol. All of the participants were capable of following instructions and reaching complete muscle relaxation; if, however the data was corrupted by patient movement, the protocol was restarted and the initial recording was rejected.

**Statistical analysis**

Linear regression and stepwise multiple regression analysis (including all variables with a \( p < 0.100 \) at univariate analysis) were used to characterize the relationship between serum GFAP and demographic characteristics (age, age at onset, sex and mutation status). Differences in clinical variables and biomarker concentrations were assessed with one-way analysis of covariance (ANCOVA), corrected for age, sex and/or mutation status, with Bonferroni multiple comparisons correction. Pearson’s correlations were used to assess associations between serum GFAP, age and education corrected clinical variables and TMS measures. Survival was calculated as time from symptom onset to time of death from any cause (outcome=0) or censoring date (outcome=1). Survival analysis was carried out by the Kaplan-Meier method with log rank post hoc testing and by means of univariate stepwise Cox proportional-hazard regression analysis; hazard ratios (HR) are provided with their respective 95% confidence intervals (CIs). A two-sided \( p \)-value<0.05 was considered significant and corrected for multiple comparisons using false discovery rate (FDR) when appropriate. Statistical analyses were performed using SPSS (v.24; SPSS, IBM).
Data availability

All study data, including raw and analysed data, and materials will be available from the corresponding author, B.B., upon reasonable request.
Results

Participant characteristics

Baseline demographics, clinical variables and GFAP levels are reported in Table 1.

In the FTLD group, serum GFAP concentration correlated with age ($\beta=0.22$, $p<0.001$), age at onset ($\beta=0.20$, $p=0.001$), and female sex ($\beta=0.20$, $p=0.001$), but did not correlate with the presence of a pathogenic mutation ($\beta=-0.05$, $p=0.447$) at the linear regression analysis. In the stepwise multiple regression model, GFAP concentration correlated with both age ($\beta=0.20$, $p=0.001$) and female sex ($\beta=0.18$, $p=0.003$). Serum GFAP concentration was significantly higher in females (mean±SE, n=129, 380.7±22.1pg/mL) compared with males (mean±SE, n=153, 288.2±17.0 pg/mL, $p=0.001$), also after correcting for age ($p=0.003$), phenotype ($p=0.001$), or both ($p=0.002$). We observed comparable levels of serum GFAP in both sporadic FTLD (mean±SE, n=250, 334.2±15.4) and in patients with GRN mutations (mean±SE, n=30, 307.4±26.4), while lower levels were observed in MAPT mutation carriers (mean±SE, n=2, 202.1±18.4).

Serum GFAP concentrations in FTLD subgroups

Serum GFAP concentrations were significantly increased in most FTLD subgroups (age- and sex-corrected ANCOVA, $F(8,397)=13.57$, $p<0.001$, $\eta^2=0.22$). In Bonferroni-corrected post hoc tests, we observed significant increases in serum GFAP concentration in bvFTD, avPPA, svPPA, and CBS compared with HC. Patients with avPPA had significantly higher serum GFAP concentration compared with CBS and PSP. We did not observe significant differences in GFAP concentration between any FTLD subgroup and AD (see Table 1 and Figure 1).

Serum GFAP associations with disease severity in FTLD

Cognitive and behavioural assessment. Serum GFAP concentration showed significant associations with baseline BADL ($r=0.21$, $p=0.001$), IADL ($r=0.28$, $p<0.001$) and FTLD-modified CDR sum of
boxes ($r=0.27$, $p<0.001$); the higher the serum GFAP level, the greater impairment in functional activities and disease severity (see Figure 2). Significant correlations were observed between serum GFAP concentration and MMSE score ($r=-0.38$, $p<0.001$), phonemic ($r=-0.16$, $p=0.033$) and semantic fluency ($r=-0.28$, $p<0.001$), clock drawing ($r=-0.32$, $p<0.001$), trail-making part A ($r=-0.29$, $p<0.001$) and B ($r=-0.33$, $p<0.001$), and token test ($r=-0.29$, $p<0.001$), with higher levels of serum GFAP correlating with poorer scores (see Figure 2).

No significant correlations were observed for the Rey figure copy ($r=-0.13$, $p=0.114$) and recall ($r=-0.06$, $p=0.437$), short story ($r=-0.13$, $p=0.127$), and digit symbol ($r=-0.11$, $p=0.158$).

Neuropsychiatric and behavioural disturbances, evaluated with the FBI, did not correlate with serum GFAP concentration ($r=0.11$, $p=0.087$).

All tests were age- and education- corrected; FDR-adjusted $p$-values for multiple comparisons are reported for each test.

Brain imaging. Serum GFAP concentration correlated neither with grey matter atrophy nor with white matter hyperintensities burden at the pre-established threshold ($p<0.05$, whole-brain FDR-corrected).

TMS measures. TMS measures were performed to evaluate average SICI, ICF, LICI and SAI. In the FTLD group ($n=87$), serum GFAP concentration was significantly associated with LICI ($r=0.31$, $p=0.016$) (see Figure 3), but not with SICI, ICF or SAI.

Interestingly, in the AD group ($n=12$), we observed a significant association between serum GFAP and average SAI ($r=0.678$, $p=0.015$).

Reported $p$-values are FDR-adjusted for multiple comparisons.

**Serum GFAP associations with prognosis in FTLD**
Serum GFAP concentration did not predict survival in FTLD patients. At the univariate Cox regression analysis there was no significant association between survival and serum GFAP concentration (HR 1.00 95% CI 0.99-1.00, p=0.866). Patients with high serum GFAP levels (upper than median values) did not have shorter survival than those with low serum GFAP levels (lower than median values) according to Kaplan-Meier survival curves (p=0.621).
**Discussion**

In this work, we confirmed and extended previous literature showing increased serum GFAP levels in most FTLD subgroups, including both the behavioural and language variants of FTD, CBS, but not in PSP. Similarly, previous reports have shown that GFAP levels are increased in CSF and plasma of sporadic FTD patients (Abu-Rumeileh et al., 2019; Ishiki et al., 2016; Marelli et al., 2020; Oeckl et al., 2019b) and in plasma of symptomatic granulin-associated FTD (Heller et al., 2020; Sudre et al., 2019). On the contrary, several reports have shown that PSP patients have only slightly, non-significantly increased CSF levels of GFAP compared to healthy controls (Constantinescu et al., 2010, 2009; Holmberg et al., 1998; Süssmuth et al., 2010).

Interestingly, we observed significantly higher levels of serum GFAP in females than in males. Animal models have shown that GFAP expression is highly dependent on sex hormones, and differences have been detected between males and females in the hippocampus, striatum and cerebellum (Arias et al., 2009). However, to the best of our knowledge, no other human study has identified sex-associated differences in GFAP expression so far.

We observed comparable concentrations of GFAP in sporadic FTLD and GRN mutation carriers, while patients with MAPT mutations, although assessed in only few patients, showed lower levels, confirming previous studies reporting raised GFAP concentration as a specific feature of GRN-related FTD among the different pathogenic mutations.

GFAP concentration in FTLD was associated with disease severity and disability, and correlated with deficits in several cognitive domains, in particular of executive functions and language. We also observed an association between serum GFAP concentration and indirect measures of GABAergic neurotransmission, which have been demonstrated to be impaired in FTLD (Benussi et al., 2019a, 2018; Padovani et al., 2018), and reflect disease severity and progression (Benussi et al., 2020b, 2020a). We observed that the higher the serum GFAP concentration, the greater was the impairment in LICI, which is considered to reflect short-lasting postsynaptic inhibition mediated through the GABA_B receptors at the level of local interneurons (Rossini et al., 2015; Ziemann et al.,
This is in line with the existence of dynamic GABAergic-astrocyte communication, GFAP being a major component of the astrocytic cytoskeleton (Mederos and Perea, 2019; Robel and Sontheimer, 2016).

Conversely, as compared to FTD due to GRN mutations (Sudre et al., 2019), we failed to find an association between serum GFAP and either grey matter atrophy or white matter hyperintensities burden. This may be due to the more heterogeneous FTLD group herein considered in term of both clinical phenotypes and underlying proteinopathies.

However, altogether these findings strongly support the notion that serum GFAP concentration is a marker of disease intensity and severity, in a disorder where there is urgent need to find not only diagnostic but also prognostic markers. Indeed, biological markers of disease severity are critical for advising patients and caregivers, for evaluating potential disease modifying treatments in homogeneous groups, independently of clinical phenotype, and to better understand the disease pathophysiology.

Compared with AD, FTLD is clinically heterogeneous, with patients presenting a combination of behavioural disturbances, impairment of executive functions or language deficits. Available standardised neuropsychological and clinical assessments may not be ideal in detecting the effects of future treatments, particularly in the early disease stages and across different FTLD subtypes. A non-invasive and easy to perform peripheral biomarker may represent a practical and valuable choice to assess disease severity and to categorize patients into disease subgroups.

Increased GFAP levels have been observed also after stroke (Dvorak et al., 2009) and brain injury (Papa et al., 2014), but also in neurodegenerative processes with astrogliosis. In this context, increased GFAP levels have been reported in AD (Abu-Rumeileh et al., 2019; Ishiki et al., 2016; Oeckl et al., 2019a; Olsson et al., 2016), ALS (Oeckl et al., 2019b), but also in healthy ageing (Vågberg et al., 2015). Indeed, GFAP concentrations have been shown to increase with age, similarly to what has been observed in our study, further highlighting the importance of taking age into account when interpreting plasma GFAP results.
Major strengths of our study are the large series of FTLD patients and the comprehensive approach in correlating clinical, imaging and neurophysiological data with GFAP levels, carried out at the same study site to minimize variability. A weakness of the study is the lack of autopsy confirmation, which prevented correlations between serum GFAP and FTLD-related proteinopathies. Secondly, longitudinal serum GFAP measurements were not available, and we were not able to draw conclusions on possible changes throughout disease progression.

In conclusion, serum GFAP concentration is associated with disease intensity and severity in FTLD, and may represent an accessible and repeatable biomarker to monitor disease progression and response to disease-modifying therapies in upcoming clinical trials.
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Disclosures

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg, all unrelated to the work presented in this paper. KB has served as a consultant or at advisory boards for Abcam, Axon, Biogen, Lilly, MagQu, Novartis and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg, all unrelated to the work presented in this paper.
References


## Table 1. Demographic and clinical characteristics of FTLD patients and controls

<table>
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<tr>
<th>Variable</th>
<th>bvFTD</th>
<th>avPPA</th>
<th>svPPA</th>
<th>CBS</th>
<th>PSP</th>
<th>AD</th>
<th>HC</th>
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<tr>
<td>Number</td>
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<td>48</td>
<td>24</td>
<td>50</td>
<td>30</td>
<td>63</td>
<td>61</td>
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<tr>
<td>Age, years</td>
<td>64.5±8.1</td>
<td>67.9±9.0</td>
<td>63.1±7.7</td>
<td>66.1±7.4</td>
<td>73.6±6.4</td>
<td>75.5±8.1</td>
<td>65.5±12.3</td>
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<tr>
<td>Sex, female %</td>
<td>58.2</td>
<td>43.8</td>
<td>59.3</td>
<td>52.9</td>
<td>51.6</td>
<td>31.7</td>
<td>20.6</td>
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<tr>
<td>Age at onset, years</td>
<td>61.4±7.8</td>
<td>64.9±8.7</td>
<td>60.1±7.7</td>
<td>63.5±7.3</td>
<td>69.4±6.5</td>
<td>74.0±8.3</td>
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<td>Monogenic disease, %</td>
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<td>0.0</td>
<td>2.3</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
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### Serum GFAP (pg/mL)

<table>
<thead>
<tr>
<th></th>
<th>mean±SE</th>
<th>lower-upper bound</th>
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<tbody>
<tr>
<td>FTLD</td>
<td>327.6±19.4</td>
<td>58.4-1443.4</td>
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<tr>
<td>avPPA</td>
<td>441.4±42.4</td>
<td>20.7-1397.8</td>
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<td>svPPA</td>
<td>320.8±48.9</td>
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<td>291.9±30.4</td>
<td>57.9-1024.2</td>
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<tr>
<td>PSP</td>
<td>19.1±22.8</td>
<td>20.7-652.1</td>
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<tr>
<td>AD</td>
<td>394.8±22.2</td>
<td>159.1-920.1</td>
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<tr>
<td>HC</td>
<td>183.1±12.0</td>
<td>51.6-574.9</td>
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FTLD = Frontotemporal Lobar degeneration; bvFTD = behavioural variant frontotemporal dementia; avPPA = agrammatic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; AD = Alzheimer’s disease; HC = healthy controls; GFAP = glial fibrillary acidic protein; SE = standard error.

Results are expressed as mean±standard deviations, unless otherwise specified. Monogenic disease: all *GRN* mutations, but 3 *MAPT* mutations (2 bvFTD and 1 CBS).
Legend to Figures

Figure 1. Serum biomarkers concentrations in participants by clinical diagnosis.
Serum GFAP concentrations (pg/mL) in participants by clinical diagnosis. bvFTD = behavioural variant frontotemporal dementia; avPPA = agrammatic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; AD = Alzheimer’s disease; HC = healthy controls. Bar graphs represent mean values and error bars represent 95% confidence intervals. *p<0.050; **p<0.010; ***p<0.001 after Bonferroni corrected post hoc tests.

Figure 2. Significant association between serum GFAP and neuropsychological assessment.
Association between serum GFAP concentrations (pg/mL) and (A) FTLD-CDR, (B) phonemic fluencies, (C) semantic fluencies, and (D) token test. GFAP = glial fibrillary acidic protein; FTLD-CDR = frontotemporal lobar degeneration-modified clinical dementia rating sum of boxes; IADL = instrumental activities of daily living.

Figure 3. Significant associations between serum biomarkers and neurophysiological measures.
Association between serum GFAP concentrations (pg/mL) and average LICI (ISI 50, 100, 150 ms ISI). GFAP = glial fibrillary acidic protein; SICI = short-interval intracortical inhibition; LICI = long-interval intracortical inhibition; SAI = short latency afferent inhibition; ISI = interstimulus interval.