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Original research

Plasma inflammation for predicting phenotypic conversion and clinical progression of autosomal dominant frontotemporal lobar degeneration

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ABSTRACT

Background Measuring systemic inflammatory markers may improve clinical prognosis and help identify targetable pathways for treatment in patients with autosomal dominant forms of frontotemporal lobar degeneration (FTLD).

Methods We measured plasma concentrations of IL-6, TNFα and YKL-40 in pathogenic variant carriers (*MAPT, C9orf72, GRN*) and non-carrier family members enrolled in the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration consortium. We evaluated associations between baseline plasma inflammation and rate of clinical and neuroimaging changes (linear mixed effects models with standardised (z) outcomes). We compared inflammation between asymptomatic carriers who remained clinically normal ('asymptomatic non-converters') and those who became symptomatic ('asymptomatic converters') using area under the curve analyses. Discrimination accuracy was compared with that of plasma neurofilament light chain (NfL).

Results We studied 394 participants (non-carriers=143, *C9orf72*=117, *GRN*=62, *MAPT*=72). In *MAPT*, higher TNFα was associated with faster functional decline (B=0.12 (0.02, 0.22), p=0.02) and temporal lobe atrophy. In *C9orf72*, higher TNFα was associated with faster functional decline (B=0.09 (0.03, 0.16), p=0.006) and cognitive decline (B=−0.16 (−0.22, −0.10), p<0.001), while higher IL-6 was associated with faster functional decline (B=0.12 (0.03, 0.21), p=0.01). TNFα was higher in asymptomatic converters than non-converters (β=0.29 (0.09, 0.48), p=0.004) and improved discriminability compared with plasma NfL alone (ΔR^2=0.16, p=0.007; NfL: OR=1.4 (1.03, 1.9), p=0.03; TNFα: OR=7.7 (1.7, 31.7), p=0.007).

Conclusions Systemic proinflammatory protein measurement, particularly TNFα, may improve clinical prognosis in autosomal dominant FTLD pathogenic variant carriers who are not yet exhibiting severe impairment. Integrating TNFα with markers of neuronal dysfunction like NfL could optimise detection of impending symptom conversion in asymptomatic pathogenic variant carriers and may help personalise therapeutic approaches.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inflammation plays a key role in neurodegenerative pathophysiology, including frontotemporal lobar degeneration.

WHAT THIS STUDY ADDS

⇒ Concentrations of plasma-based proinflammatory proteins such as TNFα relate to future clinical decline in patients with autosomal dominant forms of frontotemporal dementia. Inflammatory biomarkers may complement measures or neuronal or glial injury for optimising prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In frontotemporal dementia research, inflammatory proteins should be considered among blood biomarker panels. Pending additional studies, clinical treatments and interventions targeting inflammatory pathways may be beneficial for patients with frontotemporal dementia.

INTRODUCTION

Inflammation is a central component of neurodegenerative disease pathogenesis. Blood-based biomarkers offer easily obtainable, relatively non-invasive, and scalable measurement of systemic inflammation. Evaluating systemic inflammatory biomarkers in asymptomatic and mildly symptomatic disease stages may help improve prognosis and further characterise the role of peripheral immune activation in neurodegenerative disease. Individuals with autosomal dominant pathogenic variants causing frontotemporal lobar degeneration (FTLD) represent a unique model for studying whether systemic inflammatory biomarkers have clinical utility.

FTLD is among the most common causes of dementia in adults under 65 years old.[1] Up to 40% of FTLD cases have a family history of dementia

and around 10% have an autosomal dominant inheritance.[2] Most identified inherited FTLD cases are caused by a pathogenic variant of one of three genes: chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), or microtubule associated protein tau (*MAPT*).[3] In vivo and in vitro models suggest both central and systemic inflammatory pathways may impact the severity of neurodegeneration in FTLD.[4–9] In FTLD patients with pathogenic *GRN* variants, blood biomarkers of immune function correlate with clinical severity and brain structure, especially white matter.[9] Additionally, systemic autoimmune diseases are disproportionately prevalent in FTLD patients compared with healthy controls and patients with Alzheimer's disease.[10 11] Few clinical studies have evaluated the role of peripheral inflammation on FTLD disease progression in humans. Quantification of key markers reflecting inflammatory state may help identify targetable pathways for treatment and inform utility of plasma inflammatory biomarkers to aid disease conversion and prognosis.

Most recent research has focused on biomarkers sensitive to neuronal degeneration in FTLD. Accumulating evidence supports plasma neurofilament light chain (NfL) as a candidate biomarker for FTLD diagnosis, prognosis, and treatment response measurement.[12 13] Plasma inflammatory markers have not been studied in familial FTLD patients followed longitudinally from asymptomatic to symptomatic disease stages.[14] Identifying associations with symptom conversion and clinically meaningful FTLD outcomes like daily functioning, behaviour, and cognition might support the use of systemic inflammation measurement alongside markers of neuronal and glial dysfunction.[12 14 15]

We assessed three proteins with widespread and broadly influential roles across inflammatory pathways—IL-6, YKL-40, TNFα—in plasma collected from autosomal dominant FTLD pathogenic variant carriers and controls (non-carrier family members) followed longitudinally in the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) consortium. We investigated (A) plasma inflammation levels between genetic groups (*MAPT, C9orf72, GRN*), (B) whether baseline plasma inflammation levels related to rates of change in clinical functioning and brain volume, (C) the ability of inflammatory markers to discriminate stable asymptomatic participants from those who phenoconvert to symptomatic disease and (D) the added prognostic value of pairing plasma inflammation levels with plasma NfL to identify asymptomatic converters.

METHODS

Additional methods and references for subsequent sections are provided in online supplemental material.

Participants

The study included 394 participants in the ALLFTD consortium (ClinicalTrials.gov NCT04363684), which enrols individuals based on a family history suggestive of familial FTLD. Only participants with pathogenic *C9orf72* (N=117), *GRN* (N=62), or *MAPT* (N=72) variants, or non-carrier family members (N=143) were included in the analyses reported here. Genetic screening methods are described in detail elsewhere.[16] All non-carriers were functionally normal at baseline based on a global score of 0 using the Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center (NACC) FTLD module (CDR+NACC FTLD; see below). Clinical phenotype frequency for each genetic group is shown in table 1.

Converters versus non-converters

To inform clinical utility of inflammatory biomarkers, we used longitudinal clinical data (minimum 2 study visits, max=6) to define baseline subgroups based on their future disease trajectory. Clinical disease severity was defined using the CDR+NACC FTLD global score.[17] Asymptomatic non-converter pathogenic variant carriers (N=90) were clinically normal at all study visits (CDR+NACC FTLD Global=0). Asymptomatic converters (N=19) were clinically normal at baseline and exhibited at least mild behavioural or cognitive changes at their last study visit (CDR+NACC FTLD Global >0).

Plasma collection and protein measurement

Blood samples were collected and stored following standardised procedures for the ALLFTD consortium. Plasma IL-6, YKL-40, and TNFα concentrations were quantified in duplicate using Meso Scale Discovery (Acrobiosystems, Newark, Delaware, USA) chemiluminescence assays. All participants had at least one inflammatory biomarker measured (IL-6, N=375; YKL-40, N=394; TNFα, N=389). Samples with coefficient of variation

Table 1 Frequency of clinical phenotype diagnoses across autosomal dominant mutation carriers and non-mutation carrier family members

	Non-carrier kindred	Pathogenic variant carriers	*C9orf72*	*GRN*	*MAPT*
N	143	251	117	62	72
Clinically normal	140 (98)	120 (48)	51 (44)	32 (52)	37 (51)
bvFTD	0 (0)	60 (24)	30 (26)	6 (10)	24 (33)
MBI	0 (0)	12 (5)	4 (3)	5 (8)	3 (4)
AD-Dementia	0 (0)	5 (2)	1 (1)	2 (3)	2 (3)
MCI	0 (0)	14 (6)	10 (12)	2 (3)	2 (3)
nfvPPA	0 (0)	4 (2)	0 (0)	4 (6)	0 (0)
svPPA	0 (0)	2 (1)	1 (1)	1 (2)	0 (0)
lvPPA	0 (0)	1 (<1)	0 (0)	1 (2)	0 (0)
FTD/ALS	0 (0)	13 (5)	13 (11)	0 (0)	0 (0)
CBS	0 (0)	6 (2)	1 (1)	5 (8)	0 (0)
Primary psychiatric	3 (2)	5 (2)	2 (2)	2 (3)	1 (1)
Other	0 (0)	9 (4)	4 (3)	2 (3)	3 (4)

Data presented as raw numbers and the percentage of representation within the specific group.
AD-dementia, amnestic-predominant dementia; bvFTD, behavioural variant FTD; CBS, corticobasal syndrome; FTD/ALS, frontotemporal dementia with/without amyotrophic lateral sclerosis; lvPPA, logopenic variant primary progressive aphasia; MBI, mild behavioural impairment; MCI, mild cognitive impairment; nfvPPA, nonfluent/agrammatic variant PPA; svPPA, semantic variant primary progressive aphasia.

>25% were excluded from all analyses (IL-6, N=35; YKL-40, N=0; TNFα, N=21). A total of 334 participants had all three inflammatory biomarkers measured and eligible for analyses (non-carriers, N=120; *C9orf72*, N=98; *GRN*, N=57; *MAPT*, N=59; online supplemental table 1). As reported in a separate study from this cohort, plasma NfL concentrations were measured with single-molecule array technology (Quanterix Simoa; Lexington, Massachusetts, USA).[12]

Disease outcomes

Clinical Outcomes: Clinical Disease Severity, Socioemotional Sensitivity and Cognition

Our primary longitudinal clinical outcome was based on the CDR+NACC FTLD rating scale. The CDR+NACC FTLD is a measure of clinical disease severity optimised for FTD spectrum cohorts.[17 18] The 'Global' score categorises each participant as asymptomatic (global score=0), prodromal mild cognitive or behavioural symptoms of neurodegenerative disease[18] (global score=0.5), or clear functionally impairing symptoms consistent with dementia ('overtly symptomatic;' global score ≥1). For analysing longitudinal clinical disease severity, we used the CDR+NACC FTLD Sum of Boxes (SB) score (range 0–24; higher scores indicate worse severity).

Secondarily, we evaluated longitudinal changes in socioemotional sensitivity and cognition. Socioemotional sensitivity was measured using the Revised Self-Monitoring Scale (RSMS) total score.[19] The RSMS is completed by a study informant about the participant and measures sensitivity and responsiveness to subtle emotional expressions during face-to-face interactions. Lower scores representing more severe dysfunction (ie, less socioemotional sensitivity). Given the common early changes in executive functions in FTLD spectrum diseases, we used the NACC Uniform Data Set (V.3.0) executive function composite score (UDS3-EF) as the primary cognitive outcome.[20] Higher UDS3-EF scores reflect better executive functioning.

Brain imaging

Volumetric T1-weighted images were acquired according to the LEFFTDS protocol.[21] All T1-weighted images were visually inspected for quality control before bias field correction and segmentation. An intrasubject template was created by non-linear diffeomorphic and rigid-body registration and then a within-subject modulation was applied. A customised group template was generated from the within-subject average grey and white matter tissues and cerebrospinal fluid by non-linear registration template generation. Modulated intrasubject grey and white matter were geometrically normalised to the group template and then smoothed. Every step of the transformation was carefully inspected from the native space to the group template. Linear and non-linear transformations between the group template space and International Consortium of Brain Mapping were applied.

Data analyses

Analyses were performed using SPSS (IBM; V.25.0 andV. 27.0). Group differences in potentially confounding variables (age, sex, education as outcomes) between pathogenic variant carriers and non-carriers (predictors) were analysed with linear regression models. We further assessed differences in global cognition (Montreal Cognitive Assessment; MoCA), CDR+NACC FTLD SB, RSMS total score and UDS3-EF score, and frequency of asymptomatic status (CDR+NACC FTLD Global=0) between the three genetic groups at baseline.

Cross-sectional group comparisons

We first evaluated baseline plasma inflammation differences between pathogenic variant carriers and non-carriers and between the three genotypes using linear regression. To determine whether presence of a pathogenic variant (vs disease severity) was associated with differences in inflammatory protein levels, we compared asymptomatic non-converter pathogenic variant carriers to non-carrier family members who also had 2+ study visits (N=112). We compared inflammatory protein levels between genetic groups (*C9orf72* vs *GRN* vs *MAPT*) while controlling for disease severity (CDR+NACC FTLD SB). We then evaluated the effect of disease severity on plasma inflammatory proteins among all pathogenic variant carriers (N=251; CDR+NACC FTLD Global=0 vs 0.5 vs 1+).

Baseline inflammation and rate of functional, socioemotional, and cognitive changes

We used linear mixed effects models with random slopes and intercepts to evaluate the association between baseline inflammation levels and longitudinal changes in our clinical outcomes. Longitudinal models excluded pathogenic variant carriers with baseline CDR+NACC FTLD Global >1 to limit ceiling effects associated with severe impairment at baseline. We evaluated the interaction between baseline inflammation level and time since baseline visit (years) to estimate the longitudinal trajectory differences according to baseline inflammation level. We present standardised regression estimates controlling for baseline age, sex and years of education among pathogenic variant carriers. Each genotype was analysed in separate models. Statistical significance (p values) is reported unadjusted for multiple comparisons. Accounting for the three different clinical outcomes analysed in each model (CDR+NACC FTLD SB, RSMS total score, UDS3-EF), unadjusted p values <0.017 would survive a conservative Bonferroni correction (0.05/3=0.017).

We also aimed to inform whether significant associations between baseline inflammation and longitudinal clinical outcomes were specific to pathogenic variant carriers. We incorporated healthy non-carriers into our models and evaluated the three-way interaction between baseline inflammation level, time since baseline, and pathogenic variant status (pathogenic variant carriers vs non-carriers). A statistically significant three-way interaction would indicate that the association between baseline inflammation and longitudinal clinical outcomes observed in pathogenic variant carriers was statistically significantly stronger (or weaker) than the effect of baseline inflammation observed in non-carriers.

Models with the CDR+NACC FTLD SB as the outcome had residuals with statistically significant departures from normality (positive skew, Kolmogorov-Smirnov test p<0.001). Even though departures from normality were reduced after log transformation, we report results based on the original scale because they are more interpretable, and the pattern of results were consistent with those after transformation.

Neuroimaging analyses

Voxel-based morphometry analyses were conducted using FSL[22] for baseline visits (cross-sectional). Familywise error correction was performed using 5000 permutations with threshold free cluster enhancement[23] and models adjusted for age, sex, and total intracranial volume. Longitudinal analyses were performed in the Bayesian linear mixed-effect model framework.[24] The interaction between inflammation at baseline and rate of cortical atrophy over time was thresholded using the posterior

Table 2 Descriptive baseline characteristics for the mutation carriers and non-mutation carriers in the study

	Non-carrier kindred	Pathogenic variant carriers	Sig. (p)	*C9orf72*	*GRN*	*MAPT*	Sig. (p)
N	143	251		117	62	72	
Age, y	47.5 (13.5)	50.7 (14.15)	0.03	51.7 (14.3)	57.0 (13.2)	44.0 (13.4)	<0.001
Sex, % female	62	57	0.34	62	48	56	0.24
Education, year	15.5 (2.4)	15.4 (2.6)	0.69	15.5 (2.4)	15.4 (2.8)	15.4 (2.6)	0.98
APOE e4, % carrier	31	31	0.99	32	24	33	0.65
MoCA	27.2 (2.2)	24.0 (6.2)	<0.001	23.9 (6.1)	23.6 (6.6)	24.4 (5.8)	0.73
CDR+NACC FTLD SB	0 (0.0)	3.5 (5.5)	<0.001	3.8 (5.3)	3.1 (5.4)	3.4 (5.8)	0.75
RSMS total	46.9 (9.2)	37.2 (16.4)	<0.001	36.2 (15.7)	38.4 (4.3)	37.9 (18.8)	0.68
UDS3-EF (z)	0.4 (0.8)	−0.4 (1.3)	<.001*	−0.6 (1.3)	−0.4 (1.3)	0.0 (1.3)	.03*
CDR+NACC FTLD Global, N (%)			<0.001				0.55
0	143 (100)	126 (50)		53 (45)	35 (56)	38 (53)	
0.5	0 (0)	45 (18)		23 (20)	8 (13)	14 (19)	
Symptom duration, year	–	2 (1–4)	–	3 (1–7)	1 (0.5–1)	1.5 (0–3.5)	0.21
≥1	0 (0)	80 (32)		41 (35)	19 (31)	20 (28)	
Symptom duration, year	–	5 (3–8)	–	5 (3–8)	3 (2–4)	6 (4–14)	0.03
Progression status (2+ visits), N	112	183	–	78	47	58	0.30
Asymptomatic non-converter	112 (100)	90 (49)		41 (53)	23 (49)	26 (45)	
Asymptomatic converter	0 (0)	19 (10)		3 (4)	6 (13)	10 (17)	
Prodromal non-progressor	0 (0)	16 (9)		9 (12)	3 (6)	4 (7)	
Prodromal progressor	0 (0)	14 (8)		4 (5)	4 (9)	6 (10)	
Overtly symptomatic (all visits)	0 (0)	44 (24)		21 (27)	11 (23)	12 (21)	

Data presented as either raw frequency (percentage of group), mean (SD) or median (lower quartile-upper quartile) unless otherwise noted. 'Asymptomatic non-converters' had a CDR+NACC FTLD Global=0 at all study visits. 'Asymptomatic converters' were CDR+NACC FTLD=0 at baseline and >0.5 at their last study visit. 'Prodromal non-progressors"'were CDR+NACC FTLD=0.5 at all study visits. 'Prodromal progressors' were CDR+NACC FTLD=0.5 at baseline and >1 at their last study visit. 'Overtly symptomatic' participants were CDR+NACC FTLD ≥1 at all study visits.
*Group-level comparisons controlled for age, sex and education.
APOE, apolipoprotein E; CDR, Clinical Dementia Rating ; FTLD, frontotemporal lobar degeneration; MoCA, Montreal Cognitive Assessment; NACC, National Alzheimer's Coordinating Center; RSMS, Revised Self-Monitoring Scale; SB, sum of boxes; UDS3-EF, Uniform Data Set v3.0 Executive Function composite score.

probability maps with an alpha=5%. Neuroimaging analyses were restricted to pathogenic variant carriers and stratified by genotype given regional atrophy pattern differences expected between groups.[25 26]

Identifying asymptomatic converter pathogenic variant carriers

Among pathogenic variant carriers, we evaluated the classification accuracy of plasma inflammatory markers between asymptomatic non-converters and asymptomatic converters evaluated using area under the receiver operating characteristic curve analyses (AUC). These analyses were repeated in a subset of participants who also had plasma NfL levels measured previously. Binary logistic regression models with OR additionally adjusting for age, sex and education were used to evaluate the added value of plasma inflammatory markers beyond the expected prognostic utility of NfL.[12]

RESULTS

Descriptive differences and baseline group comparisons are provided in online supplemental results (text and online supplemental figures 1 and 2) and in table 2.

Baseline plasma inflammation associations with longitudinal disease outcomes

All genotypes

Among all pathogenic variant carriers, higher TNFα was associated with more rapid cognitive decline (B=−0.12 (−0.20, −0.05), p=0.002). Higher baseline YKL-40 was associated with faster decline in socioemotional sensitivity among all pathogenic variant carriers (B=−0.09 (−0.14, −0.04), p<0.001). All other associations between baseline plasma inflammation and longitudinal clinical or neuroimaging outcomes were not statistically significant in the combined genotype analyses (online supplemental figure 3).

MAPT

Among pathogenic *MAPT* variant carriers, higher baseline TNFα was associated with more rapid worsening of disease severity (CDR+NACC FTLD SB; B=0.12 (0.02, 0.22), p=0.02; figure 1). When including non-carriers, there was a three-way interaction, suggesting that the relationship between TNFα and disease severity trajectory was stronger in *MAPT* carriers than non-carriers (p=0.001). Higher baseline TNFα corresponded with lower inferior temporal lobe volume (predominantly left) at baseline and a faster rate of brain volume loss in widespread cortical regions including, but not limited to, the temporal lobes (online supplemental figure 4).

C9orf72

Among pathogenic *C9orf72* carriers, higher TNFα was associated with more rapid worsening of disease severity (B=0.09 (0.03, 0.16), p=0.006) and cognitive decline (B=−0.16 (−0.22, −0.10), p<0.001). Higher baseline IL-6 was associated with steeper decline in disease severity (B=0.12 (0.03, 0.21), p=0.01; figure 2), and higher baseline YKL-40 was associated with faster decline in socioemotional sensitivity (B=−0.42 (−0.67, −0.17), p=0.001). Again, when including non-carriers, effects evidenced a three-way interaction such that estimates were significantly

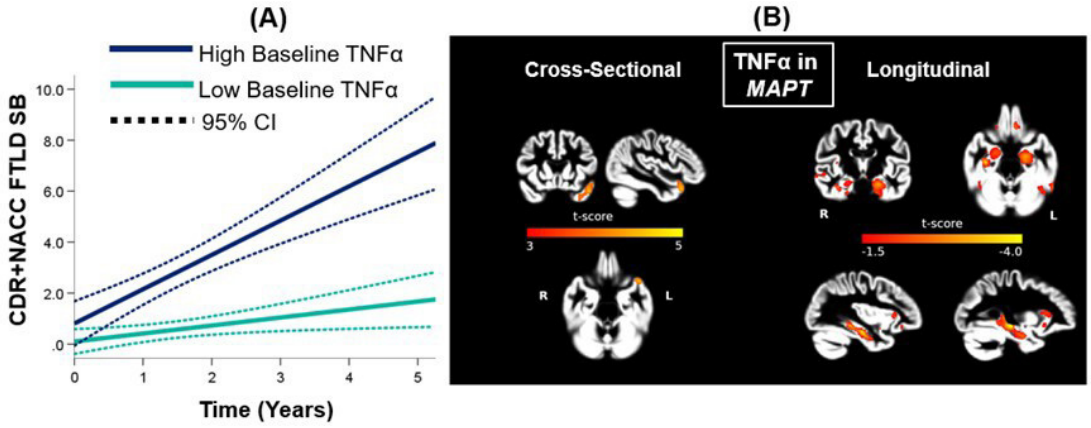

Figure 1 Association of baseline plasma TNFα with rate of change in disease severity among pathogenic *MAPT* variant carriers. (A) Participants with high baseline TNFα (>75th percentile, blue line) had a more rapid clinical disease progression (CDR+NACC FTLD sum of box score increase) over time than those with low baseline TNFα (<25th percentile, green line). (B) At baseline (cross-sectionally), voxel-based morphometry analysis revealed higher plasma TNFα was associated with lower brain volume in the left anterior temporal lobe (blue=p<0.05 after familywise error correction using 5000 permutations with threshold-free cluster enhancement. Longitudinally, Bayesian linear mixed-effects analyses revealed widespread regions where higher baseline plasma TNFα was associated with significantly faster atrophy rates, with the most rapid atrophy (red areas) occurring in medial temporal structures (threshold using posterior probability maps and p<0.05 alpha). CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; NACC, National Alzheimer's Coordinating Center; SB, Sum of Boxes.

stronger in *C9orf72* carriers than in non-carriers. Inflammatory markers did not strongly correlate with brain volume trajectories, though we saw a trend-level association (p<0.1) of higher IL-6 with lower brain volume in dorsal and lateral parietal lobes (predominantly left) at baseline (cross-sectionally; (online supplemental figure 5).

GRN

Among pathogenic *GRN* variant carriers, higher baseline YKL-40 was associated with faster decline in socioemotional sensitivity (B=−0.08 (−0.15, −0.01), p=0.04), though IL-6 and TNFα did not correlate with clinical trajectories in *GRN* carriers. Higher baseline IL-6 associated with faster rates of longitudinal atrophy in clusters predominantly within the insula and temporal lobes (online supplemental figure 6), but no other inflammatory marker evidenced a statistically significant association with grey matter atrophy in the *GRN* group.

All associations between baseline plasma inflammatory marker concentrations and longitudinal clinical outcomes for each gene group are shown in online supplemental figures 7–9.

Non-converters versus converters

Plasma TNFα was significantly higher in converters than non-converters (β=0.29 (0.09, 0.48), p=0.004; figure 3A). Converters, on average, had longer study follow-up than non-converters (~6 months). Baseline plasma TNFα levels

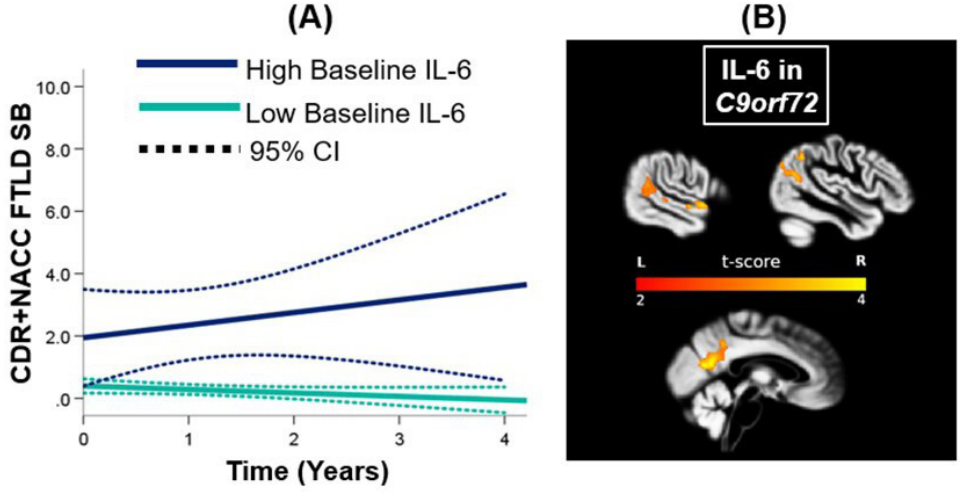

Figure 2 Association baseline plasma IL-6 with rate of change in disease severity among pathogenic *C9orf72* variant carriers. (A) Participants with high baseline IL-6 (>75th percentile, blue line) had a more rapid clinical disease progression (CDR+NACC FTLD sum of box score increase) over time than those with low baseline IL-6 (<25th percentile, green line). (B) At baseline (cross-sectionally), voxel-based morphometry analyses revealed regions with a trend towards an association of higher IL-6 with lower brain volume predominantly in lateral parietal and medial parietal/precuneus regions (blue=p<0.10 after familywise error correction using 5000 permutations with threshold-free cluster enhancement). Bayesian linear mixed-effects analyses did not support a significant association of baseline plasma IL-6 concentrations with the rates of brain atrophy longitudinally. CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; NACC, National Alzheimer's Coordinating Center; SB, Sum of Boxes.

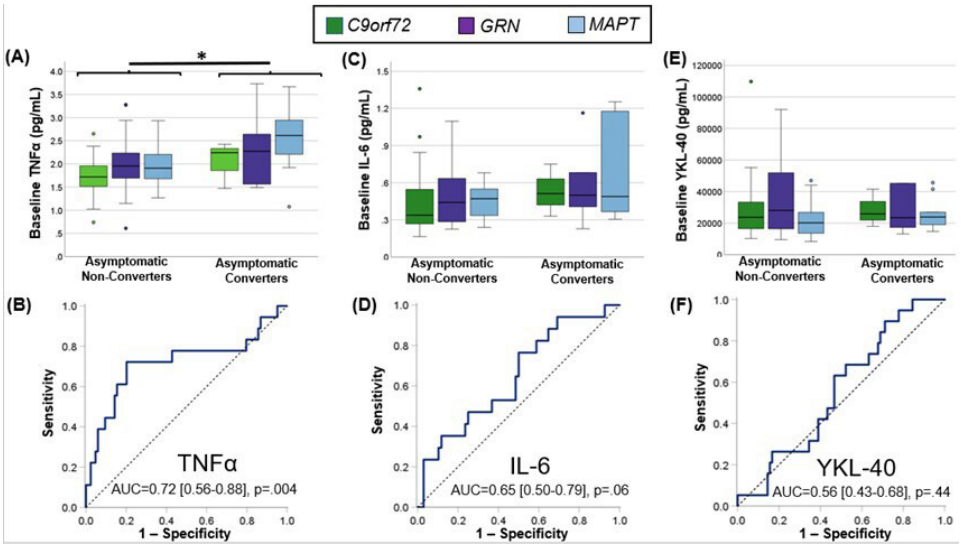

Figure 3 Baseline plasma inflammatory marker concentration differences between asymptomatic non-converter participants (CDR+NACC FTLD Global=0 at all visits) and asymptomatic converter participants (CDR+NACC FTLD Global=0 at baseline and >0.5 at a future visit). (A, B) Baseline plasma TNFα was statistically significantly higher in asymptomatic converters than asymptomatic non-converters (β=0.29 (0.09, 0.48), p=0.004) and showed fair discrimination accuracy between groups (AUC=0.72). There were no statistically significant differences in plasma IL-6 (C, D) nor YKL-40 (E, F) between asymptomatic converters and asymptomatic non-converters, and discrimination accuracy was insufficient (AUC <0.70) for both. Separate box-and-whisker plots are shown for each gene group for visualisation only (figure 4A,C,E). Gene groups were combined for all analyses. AUC, area under the curve; CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; NACC, National Alzheimer's Coordinating Centre; SB, Sum of Boxes.

showed fair discrimination of asymptomatic converters and non-converters (AUC=0.72 (0.56–0.88), p=0.004; Youden cut-off 2.2 pg/mL: 72% sensitivity, 80% specificity to detecting converters) (figure 3B). Results remained statistically significant after further adjusting for follow-up duration Neither plasma IL-6 levels (β=0.11 (−0.10, 0.32), p=0.31; figure 3C,D) nor YKL-40 levels (β=0.01 (−0.16, 0.18), p=0.9; figure 3E,F) differed statistically significantly between asymptomatic non-converters and asymptomatic converters.

In a subset of participants who also had plasma NfL levels quantified (N=13 converters, N=55 non-converters), both plasma NfL (AUC=0.80 (0.67–0.93), p=0.001) and plasma TNFα (AUC=0.75 (0.58–0.92), p=0.005) independently discriminated converters from non-converters (figure 4). The AUC for NfL and TNFα combined increased to 0.88 (0.77–0.99) (p<0.001). Plasma TNFα significantly improved classification accuracy above and beyond plasma NfL (ΔR^2=0.16) when simultaneously evaluated in a binary logistic regression model (NfL: OR=1.4 (1.03, 1.9), p=0.03; TNFα: OR=7.7 (1.7, 31.7), p=0.007).

DISCUSSION

We evaluated plasma levels of TNFα, IL-6, and YKL-40 in FTLD pathogenic variant carriers in the ALLFTD consortium. The most consistent findings related to plasma TNFα, a proinflammatory cytokine. Higher baseline plasma TNFα was associated with faster clinical progression in both *MAPT* and *C9orf72* carriers, including executive functioning decline in *C9orf72* carriers. In the *MAPT* group, higher baseline TNFα was also associated with lower inferior and medial temporal lobe volume at baseline and more rapid atrophy rates in widespread regions longitudinally. Further, plasma TNFα discriminated converter from non-converter pathogenic variant carriers, as a whole, and improved detection of converters beyond plasma NfL alone. Collectively, study results suggest that peripheral inflammation, especially plasma TNFα, may contribute to FTLD disease pathogenesis and inform disease prognosis.

There is converging and complementary evidence that the peripheral immune system contributes to FTLD pathogenesis. For example, patients with FTLD due to transactive response DNA-binding protein 43 aggregation (FTLD-TDP) have a higher

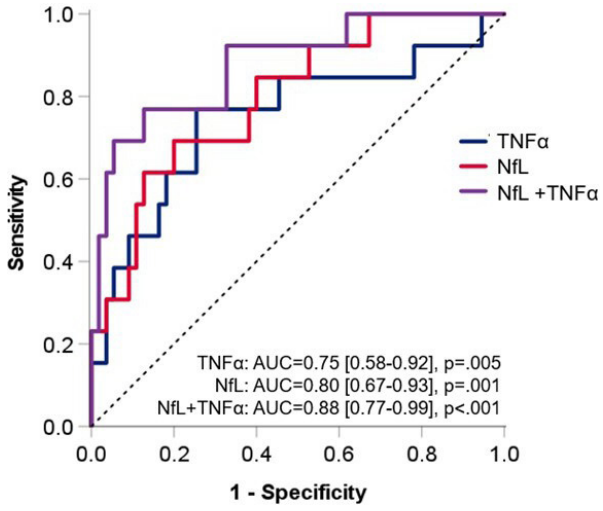

Figure 4 Added value of plasma TNFα to plasma NfL for discriminating asymptomatic converters from asymptomatic non-converters (all three gene groups combined). In a subset of participants with both markers (N=13 converters, N=55 non-converters), both plasma NfL (AUC=0.80) and plasma TNFα (AUC=0.75) independently discriminated asymptomatic converters from non-converters. The AUC for NfL and TNFα combined increased to 0.88. There was a statistically significant increase in classification accuracy after adding plasma TNFα to the model with plasma NfL only (ΔR^2=0.16; NfL: OR=1.4 (1.03, 1.9), p=0.03; TNFα: OR=7.7 (1.7, 31.7), p=0.007). AUC, area under the curve; NfL, neurofilament light.

frequency of systemic autoimmune disorders like inflammatory arthritis, cutaneous disorders, and gastrointestinal conditions.[10 11] However, others have reported lower frequency of autoimmune diseases in *C9orf72* carriers than non-carriers.[27] Of note, associations between peripheral inflammation levels and longitudinal markers of clinical disease severity were relatively consistent among the *C9orf72* group, a pathogenic variant associated with FTLD-TDP pathology. Prior work in *C9orf72* implicates other pro- (RANTES, MCP-1) and anti-inflammatory (IL-10) markers relating to different disease trajectories and clinical profiles.[28]

Correlations between baseline inflammation and brain atrophy reflected previously reported patterns of regional volume loss and atrophy rates across the different gene variants. Strongest associations were noted for higher baseline TNFα with lower temporal lobe volume in the *MAPT* group at baseline, and with faster rate of atrophy in widespread cortical regions longitudinally. *MAPT* pathogenic variant carriers have accelerated volume loss initially in temporal regions during the asymptomatic and prodromal disease stage, followed by global spread with symptom progression.[26] In *C9orf72*, we only saw an association of baseline inflammation (IL-6) and lower brain volume cross-sectionally in dorsal and lateral parietal lobes, a region implicated in other studies of *C9orf72* expansion carriers.[29] The lack of statistically significant association with longitudinal atrophy rates may be due to the minimal increase in *rate* of atrophy among *C9orf72* expansion carriers as symptoms progress.[26] It may be that our study was best powered to detect effects in the *MAPT* group due to the particularly rapid atrophy compared with *C9orf72* or *GRN* carriers.

Blood-based inflammatory protein levels do not solely or completely reflect neuroinflammation in the brain.[30] There likely are bidirectional influences of the peripheral-central immune responses. Microglia regulate the brain's immune response by functioning along a phenotypic spectrum spanning a surveillant, phagocytic state to an activated, proinflammatory state.[31] Animal models show that peripheral inflammation can lead to microglial activation via monocyte infiltration across the blood–brain barrier.[8] Activated microglia also recruit peripheral monocytes in response to brain injury or disease.[5 6 31] This may be particularly relevant for patients with pathogenic variants of *C9orf72* or *MAPT*. C9 expression is higher in microglia than other cell types and plays a direct role in immune response homeostasis, but C9-deficient microglia observed in pathogenic variants of *C9orf72* are associated with a proinflammatory phenotype.[5 6] Pathogenic *MAPT* is also linked with microglial activation and excessive production of proinflammatory mediators[32], and TNFα inhibitors may reduce microgliosis and neuronal loss in transgenic mouse models of tauopathy.[33]

We did not find statistically significant evidence of plasma cytokines (TNFα, IL-6 or YKL-40) being elevated in asymptomatic pathogenic variant carriers compared with healthy, non-carrier family members, underscoring the diagnostic limitations of plasma inflammatory biomarkers. However, a prognostic biomarker that accurately identifies asymptomatic carrier patients at-risk for nearer term symptomatic conversion would be valuable both to inform clinical prognosis and to refine clinical trial enrolment. Patients and their families may also be able to use such information to inform longer-term care planning. Towards this end, we found that plasma TNFα was elevated in patients with mild symptoms compared with asymptomatic carriers, and that higher baseline plasma TNFα differentiated asymptomatic converters from non-converters. Further, while plasma NfL has shown promise for identifying converters while asymptomatic,[12 13] we demonstrate incremental improvement when pairing plasma TNFα with NfL. FTLD prognosis and disease monitoring may ultimately be optimised through a patient-specific prediction model that combines relevant blood-based biomarkers,[12 15] brain atrophy patterns,[25 26 29] cognitive testing,[34] and behavioural characterisation.[35]

Lack of consistent associations between inflammatory markers and neurobehavioural outcomes in the *GRN* pathogenic variant carriers was unexpected given the well-established impact of *GRN* haploinsufficiency on inflammatory pathways.[36 37] In *GRN*, peripheral markers of key regulators within monocyte activation pathways were shown previously to be elevated cross-sectionally compared with controls and associated with worse white matter integrity.[9] Inconsistent findings between genetic groups in our study may partly reflect the specific inflammation markers studied, variability in clinical phenotypes, or the clinical outcomes used. For example, the *GRN* group had the greatest diversity of clinical phenotypes and the lowest proportion of patients diagnosed with bvFTD. Scales like the CDR+NACCFTLD and RSMS that rely on caregiver report may be more sensitive to behavioural changes observed in bvFTD than the breadth of cognitive changes associated with other *GRN* clinical phenotypes.[38]

Lastly, the relevance of peripheral inflammation for FTLD pathogenesis could provide insights regarding therapeutic interventions aiming to slow symptom progression. Both emerging pharmacological (eg, CSF1R inhibitors) and behavioural modifications of inflammatory pathways may be relevant in FTLD. For instance, physical activity, which is linked with lower inflammation, is associated with slower clinical decline in autosomal dominant FTLD.[39] These findings highlight avenues for future research examining whether systemic inflammation mediates the benefits of lifestyle interventions on symptom progression in FTLD. Other interventions modulating inflammatory response, including those targeting peripheral mechanisms like the gut–brain axis, may also be beneficial.[40] Additional work is needed to identify patients who would benefit most and to optimise intervention timing.

The longitudinal clinical characterisation of asymptomatic and symptomatic autosomal dominant FTLD pathogenic variant carriers is a key strength of the ALLFTD consortium. Regarding study limitations, autosomal dominant FTLD pathogenic variants are rare, so our sample size was modest, especially for analyses of specific gene groups and incorporating three-way interactions with non-carrier family members. We did not have a replication cohort and focused on just a subset of possible inflammatory markers. Plasma inflammatory markers are neither disease-specific nor necessarily direct measures of neuroinflammation. Potentially important details like co-occurring inflammatory or autoimmune conditions, or the use of anti-inflammatory medications, were not known but may influence either the measurement of blood-based inflammation markers or independently contribute to disease progression. Plasma inflammatory biomarker levels may not be as stable as other protein measurements (eg, NfL) and several other factors, such as time of day when samples were obtained, may contribute to measurement variability and secretion dynamics. Future work pairing plasma with cerebrospinal fluid could help contextualise these findings. The inflammatory proteins were measured at a single time point to assess prognostic value. Longitudinal measurement would improve our understanding of disease-related biomarker dynamics or potential for treatment response indicators. Larger longitudinal samples with similar follow-up duration would reduce bias associated with defining baseline cohorts (ie, asymptomatic converters and non-converters) using post-baseline data.

Our sample was predominantly white/Caucasian and results may not generalise to patient groups more racially/ethnically representative of the increasing sociodemographic diversity of the ageing population.

Conclusions

Systemic inflammatory protein measurement may improve clinical prognosis in autosomal dominant FTLD pathogenic variant carriers who are not yet exhibiting severe impairment. Higher baseline systemic inflammation, particularly TNFα, may relate to with faster disease progression. Integrating TNFα with markers of neuronal dysfunction like NfL could optimise detection of impending symptom conversion in asymptomatic pathogenic variant carriers. The peripheral immune system warrants continued study as a targetable and readily measurable biological pathway.

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REFERENCES

1 Bang J, Spina S, Miller BL. Frontotemporal dementia. *The Lancet* 2015;386:1672–82.
2 Rohrer JD, Guerreiro R, Vandrovcova J, *et al*. The heritability and genetics of frontotemporal lobar degeneration. *Neurology* 2009;73:1451–6.
3 Olszewska DA, Lonergan R, Fallon EM, *et al*. Genetics of frontotemporal dementia. *Curr Neurol Neurosci Rep* 2016;16.
4 Zhao W, Beers DR, Bell S, *et al*. TDP-43 activates microglia through NF-κB and NLRP3 inflammasome. *Exp Neurol* 2015;273:24–35.
5 Lall D, Baloh RH. Microglia and c9orf72 in neuroinflammation and ALS and frontotemporal dementia. *J Clin Invest* 2017;127:3250–8.
6 Trageser KJ, Smith C, Herman FJ, *et al*. Mechanisms of immune activation by c9orf72-expansions in amyotrophic lateral sclerosis and frontotemporal dementia. *Front Neurosci* 2019;13:1298.
7 McCombe PA, Henderson RD. The role of immune and inflammatory mechanisms in ALS. *Curr Mol Med* 2011;11:246–54.
8 Xie X, Luo X, Liu N, *et al*. Monocytes, microglia, and CD200-CD200R1 signaling are essential in the transmission of inflammation from the periphery to the central nervous system. *J Neurochem* 2017;141:222–35.
9 Ljubenkov PA, Miller Z, Mumford P, *et al*. Peripheral innate immune activation correlates with disease severity in GRN haploinsufficiency. *Front Neurol* 2019;10:1004.
10 Miller ZA, Rankin KP, Graff-Radford NR, *et al*. Tdp-43 frontotemporal lobar degeneration and autoimmune disease. *J Neurol Neurosurg Psychiatry* 2013;84:956–62.
11 Miller ZA, Sturm VE, Camsari GB, *et al*. Increased prevalence of autoimmune disease within C9 and FTD/MND cohorts: completing the picture. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e301.
12 Rojas JC, Wang P, Staffaroni AM, *et al*. Plasma neurofilament light for prediction of disease progression in familial frontotemporal lobar degeneration. *Neurology* 2021;96:e2296–312.
13 Rojas JC, Karydas A, Bang J, *et al*. Plasma neurofilament light chain predicts progression in progressive supranuclear palsy. *Ann Clin Transl Neurol* 2016;3:216–25.
14 Ntymenou S, Tsantzali I, Kalamatianos T, *et al*. Blood biomarkers in frontotemporal dementia: review and meta-analysis. *Brain Sci* 2021;11:244.
15 Heller C, Foiani MS, Moore K, *et al*. Plasma glial fibrillary acidic protein is raised in progranulin-associated frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2020;91:263–70.
16 Ramos EM, Dokuru DR, Van Berlo V, *et al*. Genetic screening of a large series of North American sporadic and familial frontotemporal dementia cases. *Alzheimers Dement* 2020;16:118–30.
17 Knopman DS, Weintraub S, Pankratz VS. Language and behavior domains enhance the value of the clinical dementia rating scale. *Alzheimers Dement* 2011;7:293–9.
18 Miyagawa T, Brushaber D, Syrjanen J, *et al*. Utility of the global CDR® plus NACC FTLD rating and development of scoring rules: data from the ARTFL/LEFFTDS Consortium. *Alzheimers Dement* 2020;16:106–17.
19 Lennox RD, Wolfe RN. Revision of the self-monitoring scale. *J Pers Soc Psychol* 1984;46:1349–64.
20 Staffaroni AM, Asken BM, Casaletto KB, *et al*. Development and validation of the uniform data set (v3.0) executive function composite score (UDS3-EF). *Alzheimers Dement* 2021;17:574–83.
21 Boeve B, Bove J, Brannelly P, *et al*. The longitudinal evaluation of familial frontotemporal dementia subjects protocol: framework and methodology. *Alzheimers Dement* 2020;16:22–36.
22 Jenkinson M, Beckmann CF, Behrens TEJ, *et al*. Fsl. *Neuroimage* 2012;62:782–90.
23 Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 2009;44:83–98.
24 Ziegler G, Penny WD, Ridgway GR, *et al*. Estimating anatomical trajectories with bayesian mixed-effects modeling. *Neuroimage* 2015;121:51–68.
25 Staffaroni AM, Ljubenkov PA, Kornak J, *et al*. Longitudinal multimodal imaging and clinical endpoints for frontotemporal dementia clinical trials. *Brain* 2019;142:443–59.
26 Staffaroni AM, Goh S-Y, Cobigo Y, *et al*. Rates of brain atrophy across disease stages in familial frontotemporal dementia associated with MAPT, GRN, and c9orf72 pathogenic variants. *JAMA Netw Open* 2020;3.
27 Katisko K, Solje E, Koivisto AM, *et al*. Prevalence of immunological diseases in a finnish frontotemporal lobar degeneration cohort with the c9orf72 repeat expansion carriers and non-carriers. *J Neuroimmunol* 2018;321:29–35.
28 Katisko K, Solje E, Korhonen P, *et al*. Peripheral inflammatory markers and clinical correlations in patients with frontotemporal lobar degeneration with and without the C9orf72 repeat expansion. *J Neurol* 2020;267:76–86.
29 Staffaroni AM, Cobigo Y, Goh S-YM, *et al*. Individualized atrophy scores predict dementia onset in familial frontotemporal lobar degeneration. *Alzheimers Dement* 2020;16:37–48.
30 Bettcher BM, Johnson SC, Fitch R, *et al*. Cerebrospinal fluid and plasma levels of inflammation differentially relate to CNS markers of Alzheimer's disease pathology and neuronal damage. *J Alzheimers Dis* 2018;62:385–97.
31 Mammana S, Fagone P, Cavalli E, *et al*. The role of macrophages in neuroinflammatory and neurodegenerative pathways of Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis: pathogenetic cellular effectors and potential therapeutic targets. *Int J Mol Sci* 2018;19:831.
32 Bellucci A, Bugiani O, Ghetti B, *et al*. Presence of reactive microglia and neuroinflammatory mediators in a case of frontotemporal dementia with P301S mutation. *Neurodegener Dis* 2011;8:221–9.
33 Ou W, Yang J, Simanauskaite J, *et al*. Biologic TNF-α inhibitors reduce microgliosis, neuronal loss, and tau phosphorylation in a transgenic mouse model of tauopathy. *J Neuroinflammation* 2021;18:312:312.:.
34 Staffaroni AM, Weintraub S, Rascovsky K, *et al*. Uniform data set language measures for bvFTD and ppa diagnosis and monitoring. *Alzheimers Dement (Amst)* 2021;13:e12148.
35 Toller G, Ranasinghe K, Cobigo Y, *et al*. Revised self-monitoring scale: a potential endpoint for frontotemporal dementia clinical trials. *Neurology* 2020;94:e2384–95.
36 Cui Y, Hettinghouse A, Liu CJ. Progranulin: a conductor of receptors orchestra, a chaperone of lysosomal enzymes and a therapeutic target for multiple diseases. *Cytokine Growth Factor Rev* 2019;45:53–64.
37 Cenik B, Sephton CF, Kutluk Cenik B, *et al*. Progranulin: a proteolytically processed protein at the crossroads of inflammation and neurodegeneration. *J Biol Chem* 2012;287:32298–306.
38 Rascovsky K, Hodges JR, Knopman D, *et al*. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134(Pt 9):2456–77.
39 Casaletto KB, Staffaroni AM, Wolf A, *et al*. Active lifestyles moderate clinical outcomes in autosomal dominant frontotemporal degeneration. *Alzheimers Dement* 2020;16:91–105.
40 Burberry A, Wells MF, Limone F, *et al*. C9Orf72 suppresses systemic and neural inflammation induced by gut bacteria. *Nature* 2020;582:89–94.