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).
Results 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 (B=0.29 (0.09, 0.48), p=0.004) and improved discriminability compared with plasma NfL alone (ΔR²=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. Up to 40% of FTLD cases have a family history of dementia.
and around 10% have an autosomal dominant inheritance. 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). In vivo and in vitro models suggest both central and systemic inflammatory pathways may impact the severity of neurodegeneration in FTLD. 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. Plasma inflammatory markers have not been studied in familial FTLD patients followed longitudinally from asymptomatic to symptomatic disease stages. 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.

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 phenotype convert 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 enrolls 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. 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. Asymptomatic non-converter pathogenic variant carriers (N=90) were clinically normal at all study visits (CDR+NACCFTLD 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+NACCFTLD 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 above 10% were excluded.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Frequency of clinical phenotype diagnoses across autosomal dominant mutation carriers and non-mutation carrier family members</th>
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<tbody>
<tr>
<td></td>
<td>Non-carrier kindred</td>
</tr>
<tr>
<td>N</td>
<td>143</td>
</tr>
<tr>
<td>Clinically normal</td>
<td>140 (98)</td>
</tr>
<tr>
<td>bvFTD</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MBI</td>
<td>0 (0)</td>
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<tr>
<td>AD-Dementia</td>
<td>0 (0)</td>
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<tr>
<td>MCI</td>
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<tr>
<td>nfvPPA</td>
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</tr>
<tr>
<td>svPPA</td>
<td>0 (0)</td>
</tr>
<tr>
<td>lvPPA</td>
<td>0 (0)</td>
</tr>
<tr>
<td>FTD/ALS</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CBS</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Primary psychiatric</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
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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/agranular 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 FTLD spectrum cohorts.17,18 The ‘Global’ score categorises each participant as asymptomatic (global score=0), prodromal mild cognitive or behavioural symptoms of neurodegenerative disease (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 (V3.0) 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 intra-subject 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 intra-subject 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 and V. 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 FSL22 for baseline visits (cross-sectional). Familywise error correction was performed using 5000 permutations with threshold free cluster enhancement23 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...
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.23,24

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
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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 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.

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.
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=0.003) 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 (ΔR²=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 pro-inflammatory 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 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

**Figure 3** Baseline plasma inflammatory marker concentration differences between asymptomatic non-converter participants (CDR+NA FTLD Global=0 at all visits) and asymptomatic converter participants (CDR+NA 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 visualization 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.

**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 (ΔR²=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. However, others have reported lower frequency of autoimmune diseases in C9orf72 carriers than non-carriers. 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.

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. 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. 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. 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. 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. Animal models show that peripheral inflammation can lead to microglial activation via monocyte infiltration across the blood–brain barrier. Activated microglia also recruit peripheral monocytes in response to brain injury or disease. 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. Pathogenic MAPT is also linked with microglial activation and excessive production of proinflammatory mediators, and TNFα inhibitors may reduce microgliosis and neuronal loss in transgenic mouse models of tauopathy.

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 later 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, 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, brain atrophy patterns, cognitive testing, and behavioural characterisation.

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. 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. 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.

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. 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. 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.
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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 NIL 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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Collaborators


Contributors


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Competing interests

JCR and ICM report being site PIs for clinical trials sponsored by Eli Lilly and Eisai. BA (Appleby) receives research support from the Centers for Disease Control and Prevention, the National Institutes of Health (NIH), Ionis, Alector and the CJD Foundation; he has provided consultation to Acadia, Ionis and Sangamo. BCD is a consultant for Acadia, Alector, Arkuda, Biogen, Denali, Eisai, Genentech, Lilly, Merck, Novartis, Takeda and Wave Lifesciences; receives royalties from Cambridge University Press, Elsevier and Oxford University Press and receives grant funding from the NIA, the National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health and the Bluefield Foundation. NG has participated or is currently participating in clinical trials of anti-dementia drugs sponsored by Bristol Myers Squibb, Eli Lilly/Avid Radiopharmaceuticals, Janssen Immunotherapy, Novartis, Pfizer, Wyeth, SNIF (The Study of Nasal Insulin as a Treatment for Forgetfulness) and the A4 (The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease) trial; she receives research support from Tau Consortium and the Association for Frontotemporal Dementia and is funded by the NIH. IL reports funding support from the National Institutes of Health, the Michael J. Fox Foundation, Parkinson Foundation, Lwvy Body Association, CurePSP, Roche, Abbvie, Biogen, Centogene. EIP-Pharma, Biohaven Pharmaceuticals, Novartis, Brain Neurotherapeutics Bio and United Biopharma SRL – UCB; she is a Scientific advisor for Amydis and Rossy Center for Progressive Supranuclear Palsy University of Toronto.

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Ethics approval

This study involves human participants and was approved by Johns Hopkins Medicine IRB serves as the SINGLE IRB for the ALLFTD Consortium (CR00042454 / IRB00227492; local PI: Chiadi Onyike). All participating sites additionally obtain local IRB approvals. Participants gave informed consent to participate in the study before taking part.

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Participants

The study included 394 participants in the ALLFTD consortium. ALLFTD represents a harmonized merger of two complementary familial FTLD studies initiated in 2014: The Advancing Research and Treatment of Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFTTDS) studies. The ALLFTD consortium currently includes 23 centers across the United States and Canada (allftd.org) with 18 contributing data to this project. Sites enroll individuals based on a family history suggestive of familial FTLD, usually identified through interview of a symptomatic proband. Once a family member with a pathogenic variant is identified, other members of the family are contacted and invited to participate. Enrollees do not need to know their genetic status. Only patients with pathogenic C9orf72, GRN, or MAPT variants, or non-carrier family members, were included in the analyses reported here. Genetic screening for the three major autosomal dominant pathogenic variants plus apolipoprotein E genotyping methods are described in detail elsewhere[1].

The 394 study participants included 251 FTLD pathogenic variant carriers (C9orf72=117, GRN=62, MAPT=72) and 143 functionally normal, non-carrier family members with at least one of the three inflammation proteins (IL-6, YKL-40, TNFα) analyzed at baseline. 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 vs. Non-converters

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

Plasma Collection and Protein Measurement

Blood samples were collected and stored following standardized procedures for the ALLFTD consortium. Plasma IL-6, YKL-40, and TNFα concentrations were quantified using Meso Scale Discovery (MSD) chemiluminescence assays. IL-6 and TNFα were measured via automated multiplex (UCSF Gladstone Institute; completed June 2019) and selected from the larger set of markers for the present study given their broad relevance within systemic inflammatory pathways and both analytes were consistently quantified in the linear range of detection. YKL-40 was measured via singleplex (San Francisco VA hospital core lab; completed December 2019). All samples underwent two freeze thaw cycles during the analyte measurement process. Batch effects were minimized through sample randomization by the National Centralized
Repository for Alzheimer's Disease and Related Dementias (NCRAD) prior to shipment to UCSF.

All 394 participants had at least one inflammatory biomarker measured (IL-6, N=375; YKL-40, N=394; TNFα, N=389). Samples with coefficient of variation (CV%) >25% were excluded from all analyses (IL-6, N=35; YKL-40, N=0; TNFα, N=21). After exclusion of samples with high CV%, mean±SD CV% were 8.7±6.4% (IL-6), 1.8±1.8% (YKL-40), and 8.7±4.6% (TNFα).

Through a separate study, plasma NfL concentrations were measured with single-molecule array technology (Simoa) using the commercially available NF-light digital immunoassay kit (Quanterix, Lexington, MA), as described elsewhere[3]. Plasma samples were thawed at room temperature (1 cycle), mixed thoroughly, and centrifuged at 14,000g for 3 minutes. The supernatant was loaded onto a Quanterix HD-1 Analyzer with 1:4 specified dilution. Samples were measured in duplicate with an 8-point calibration curve tested in triplicate and 2 controls tested in duplicate. Plasma concentrations were interpolated from the calibration curve within the same batch and corrected for the dilution. All samples were quantifiable within the dynamic range of 0.69-2,000 pg/mL with average coefficient of variation of 6.2±4.3%. The samples from the subset of participants with plasma NfL data included in this study all had CV<20%.

Functional, Behavioral, and Cognitive Assessments

**Primary Clinical Outcome: Clinical Disease Severity**

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 optimized for FTD spectrum cohorts[2, 4]. It can be used to generate a “Global” score that represents a weighted average of eight functional domain scores to categorize each patient as asymptomatic (CDR+NACC FTLD Global=0), prodromal mild cognitive or behavioral symptoms of neurodegenerative disease[4] (“prodromal”; CDR+NACC FTLD Global =0.5), or clear functionally impairing symptoms consistent with dementia (“overtly symptomatic;” CDR+NACC FTLD Global >1). For analyzing longitudinal clinical disease severity, we used the CDR+NACC FTLD Sum of Boxes (SB) score (range 0 to 24; higher scores indicate worse severity).

**Secondary Clinical Outcomes: Socioemotional Sensitivity and Cognition**

We evaluated longitudinal changes in socioemotional sensitivity using the Revised Self-Monitoring Scale (RSMS) total score[5]. The RSMS is a validated 13-item questionnaire that measures sensitivity and responsiveness to subtle emotional expressions during face-to-face interactions. The questionnaire has good internal consistency, retest reliability, and construct validity[6, 7]. The RSMS was completed by an informant who was a first-degree family member or friend who had known the participant for ≥5 years. Informants rated patients on each item on a 6-point Likert scale ranging from “certainly, always false” to “certainly, always true,” with lower scores representing more severe dysfunction (i.e., less socioemotional sensitivity). The RSMS has been shown to be sensitive to progression of both socioemotional symptoms and salience network atrophy in patients with familial and non-familial forms of the behavioral variant phenotype of FTLD[8, 9]. Behavioral variant phenotypes are the most common symptom presentation in the ALLFTD cohort.

We defined cognition using the National Alzheimer's Coordinating Center Uniform Data Set (v3.0) executive function composite score (UDS3-EF)[10]. The UDS3-EF is an item response
theory-based composite derived from 7 total UDS3-EF test scores: category fluency (animals and vegetables; total correct), lexical fluency (F and L words; total correct), number span backward (total correct trials), Trail Making Test parts A and B (correct lines per minute). The cognitive domains that factor into the UDS3-EF score (e.g., mental set-shifting, verbal fluency, attention/working memory) support the potential utility as a single composite measure of the common cognitive changes observed across a range of clinical phenotypes in FTLD spectrum patients. Higher UDS3-EF scores suggest better executive functioning, and a validation study showed significantly lower scores in bvFTD patients compared to controls and other patient groups[10]. Additionally, the Montreal Cognitive assessment (MoCA) was analyzed to help characterize global cognition in the study cohort at baseline.

**Voxel-Based Morphometry**

Volumetric MPRAGE sequences acquire T1-weighted images of the entire brain (sagittal slice orientation; slice thickness = 1.2 mm; in-plane resolution = 1.0x1.0 mm; TR, TE and flip angle are vendor specific according to the LEFFTDS recommendation[11]. Before any prepossessing of the images, all T1-weighted images were visually inspected for quality control. Images with excessive motion or image artifact were excluded. T1-weighted images underwent bias field correction using N3 algorithm, and segmentation was performed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm) unified segmentation[12]. An intra-subject template was created by non-linear diffeomorphic and rigid-body registration proposed by the symmetric diffeomorphic registration for longitudinal MRI framework[13]. The intra-subject template was segmented also using SPM12's unified segmentation. A within-subject modulation was applied by multiplying the timepoints' Jacobian determinant with the intra-subject averaged tissues[14]. A customized group template was generated from the within-subject average gray and white matter tissues and cerebrospinal fluid by non-linear registration template generation using Large Deformation Diffeomorphic Metric Mapping framework[15]. Modulated intra-subject gray and white matter were geometrically normalized to the group template and then smoothed using approximately 8mm full width half maximum Gaussian kernel in the group template. Every step of the transformation was carefully inspected from the native space to the group template. For statistical purposes, linear and non-linear transformations between the group template space and International Consortium of Brain Mapping (ICBM) were applied[16]. For the cross-sectional analysis, the baseline time points were modulated by taking the determinant of the Jacobian composed transformations from the native space to the group template. We used the same smoothing kernel as previously described.

**Data Analyses**

Analyses were performed using SPSS (IBM Corporation; Versions 25.0 and 27.0). Group differences in potentially confounding variables (age, sex, education) between pathogenic variant carriers and non-carriers were analyzed with linear regression models. We further assessed differences in global cognition (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. We evaluated histograms and Q-Q plots of residuals for all regression models. Dependent variables were log transformed when there were clear departures from normality.

**Cross-sectional Group Comparisons**
We performed linear regressions to evaluate baseline plasma inflammation differences between pathogenic variant carriers and non-carriers and between the three genetic groups (dummy coded to interpret pairwise genetic group differences) controlling for age, sex, and years of education. To determine whether presence of a pathogenic variant (versus 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 also compared inflammatory protein levels among genetic groups (C9orf72 vs. GRN vs. MAPT) while additionally controlling for disease severity (CDR+NACC FTLD SB). We then specifically 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+). Effect sizes were interpreted based on standardized beta (β) estimates: 0.1 = small, 0.3 = medium, 0.5 = large.

Baseline Inflammation and Rate of Functional, Socioemotional, and Cognitive Changes

We used linear mixed effects models (restricted maximum likelihood estimation) with random slopes and intercepts (unstructured covariance) to evaluate the association between baseline inflammation levels and longitudinal changes in our primary (CDR+NACC FTLD SB) and secondary (RSMS total score, UDS3-EF score) clinical outcomes. Each participant's baseline was defined as the first study visit with an available plasma inflammation biomarker measurement. Longitudinal models excluded pathogenic variant carriers with baseline CDR+NACC FTLD Global>1 to limit ceiling effects associated with severe impairment at baseline.

Our primary goal was to determine whether baseline inflammation levels were associated with rates of change in clinical outcomes among pathogenic variant carriers. We therefore evaluated the interaction between baseline inflammation level and time since baseline visit and present unstandardized regression estimates controlling for baseline age, sex, and years of education among known pathogenic variant carriers. Each genetic group was analyzed in separate models and interpreted using Benjamini-Hochberg adjusted alpha levels (false discovery rate p<.05)[17].

Secondarily, we 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 significant three-way interaction would indicate that the association between baseline inflammation and longitudinal clinical outcomes observed in pathogenic variant carriers was significantly stronger (or weaker) than the effect of baseline inflammation observed in non-carriers. These analyses were only performed when a significant association between baseline inflammation and longitudinal clinical outcomes was first observed among pathogenic variant carriers.

Neuroimaging Analyses

The image analyses were conducted using FSL[18] for the voxel based morphometry cross sectional analysis. The familywise error correction was performed using 5000 permutations with threshold free cluster enhancement[19]. The effect, at baseline, of the inflammation markers was corrected for age, gender and total intracranial volume. The longitudinal analyses were performed in the Bayesian linear mixed-effect model framework[14]. The interaction between
rate of change and inflammation marker at base line was threshold using the posterior probability maps with an alpha = 5%. Neuroimaging analyses were restricted to pathogenic variant carriers and stratified by gene group given regional atrophy pattern differences expected between groups\[20-22\].

**Identifying Asymptomatic Converter Pathogenic Variant Carriers**

Among pathogenic variant carriers, we compared plasma inflammatory markers between asymptomatic non-converters and asymptomatic converters. Inflammatory proteins that significantly differed were then evaluated using area under the receiver operating characteristic curve analyses (AUC/ROC) in the same participants to further inform the clinical relevance of observed group-level associations. These analyses were repeated in a subset of participants who also had plasma NFL levels measured previously. Binary logistic regression models 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\[3, 23\].

Supplemental Results

Descriptive Comparisons and Baseline Differences

Pathogenic variant carriers were older than non-carriers. There were no statistically significant differences in the proportion of female participants, years of education, or frequency of apolipoprotein E e4 carriers between carriers and noncarriers. As expected, pathogenic variant carriers had significantly lower MoCA total score, higher CDR+NACC FTLD SB, lower RSMS total score, and lower UDS3-EF score than non-carriers. Within pathogenic variant carriers, age differed between genetic groups (GRN > C9orf72 > MAPT). There were no statistically significant differences across genotypes in proportion of female participants, years of education, apolipoprotein E e4 carrier frequency, MoCA total score, CDR+NACC FTLD SB, RSMS total score, or proportion of symptomatic participants at baseline (CDR+NACC FTLD Global>0). C9orf72 carriers had lower baseline UDS3-EF scores than MAPT carriers (p=.04).

Cross-Sectional Group Comparisons of Plasma Inflammation Levels

Asymptomatic non-converter pathogenic variant carriers had significantly lower baseline levels of plasma TNFα (β=.16 [-.31, -.02], p=.03) and IL-6 (β=.21 [-.34, -.06], p=.006) than non-carrier family members (data not shown). Among all pathogenic variant carriers at baseline, MAPT carriers had higher levels of IL-6 than C9orf72 (β=.17 [.01, .32], p=.03) and GRN carriers (β=.16 [.001, .33], p=.048).

Among pathogenic variant carriers, baseline inflammation levels differed based on clinical disease severity (Supplemental Figure 1). Prodromal carriers (CDR+NACC FTLD Global=0.5) had statistically significantly higher plasma TNFα levels than asymptomatic carriers (β=.16 [.02, .30], p=.02). Pathogenic variant carriers with dementia (CDR+NACC FTLD Global ≥ 1) had higher plasma IL-6 than asymptomatic carriers (β=.22 [.06, .37], p=.006).
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**Supplemental Table 1:** Number of participants with all three plasma inflammatory markers measured and eligible for analyses (N=334; 85% of total sample with at least one inflammatory marker). Across non-carrier kindred and pathogenic variant carriers, 120/143 (84%) of non-carrier kindred and 214/251 (85%) of pathogenic variant carriers had all three inflammatory markers. Refer to Table 1 for frequency of participants with at least one available inflammatory markers across individual clinical phenotypes (Clinically Normal, bvFTD, MBI, etc.).
Supplemental Figure 1: Comparison of baseline plasma inflammatory proteins among pathogenic FTLD gene variant carriers. Prodromal participants (CDR+NACC FTLD Global score = 0.5) had significantly higher plasma TNFα than asymptomatic participants (CDR+NACC FTLD Global score = 0). For plasma IL-6, overtly symptomatic participants (CDR+NACC FTLD Global score > 1.0) had significantly higher concentrations than asymptomatic participants. No group differences in plasma YKL-40 were observed between asymptomatic, prodromal, and overtly symptomatic participants. Separate box-and-whisker plots are shown for each gene group for visualization only. Gene groups were combined for analyses.
Supplemental Figure 2: Inter-correlations between plasma inflammatory markers and their association with participant age (baseline). (A) All associations between plasma inflammatory markers at baseline were statistically significant (p < .03) with small to moderate effect sizes. (B) All associations between plasma inflammatory markers and participant age were statistically significant (p < .001) and ranged from small (.17, TNFα) to relatively large (.47, YKL-40) effect sizes. These relationships were similar or slightly stronger when restricting only to pathogenic variant carriers.
Supplemental Figure 3: Associations between baseline plasma inflammatory marker concentrations and longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) for pathogenic variant carriers (all gene groups combined). Longitudinal trend lines are shown for participants with low (<25th percentile, green line) or high (>75th percentile, blue line) inflammatory marker concentrations for each of the three markers evaluated (TNFα, IL-6, YKL-40). Statistically significant associations (* p < .05) indicate where high baseline plasma inflammation was associated with more rapid clinical decline.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score.
Supplemental figure 4: Multi-slice axial views showing the association of baseline plasma TNFα concentrations with brain volume among pathogenic MAPT variant carriers. (A) At baseline (cross-sectionally), voxel-based morphometry analysis revealed that higher TNFα was associated with lower brain volume in a small region of the left anterior temporal lobe (orange = p<.05 after family-wise error correction using 5,000 permutations with threshold-free cluster enhancement). (B) Longitudinally, Bayesian linear mixed-effects (BLME) analyses revealed widespread areas where higher baseline plasma TNF-alpha was associated with significantly faster atrophy rates (warmer colors = steeper atrophy slopes; threshold using posterior probability maps and p<.05 alpha). These multi-slice images correspond with the selected representative slices presented in main Figure 1.
Supplemental figure 5: Multi-slice axial views showing the association of baseline plasma IL-6 concentrations with brain volume among pathogenic C9orf72 variant carriers. 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 (red = p<.10 after family-wise error correction using 5,000 permutations with threshold-free cluster enhancement). There was no significant association of baseline plasma IL-6 concentrations with the rates of brain atrophy longitudinally. These multi-slice images correspond with the representative slices presented in main Figure 2.
Supplemental figure 6: Multi-slice axial views showing the association of baseline plasma IL-6 concentrations with brain volume among pathogenic GRN variant carriers. Longitudinally, Bayesian linear mixed-effects (BLME) analyses revealed scattered areas in subcortical, temporal, insula, and dorsal parietal/precuneus regions where higher baseline plasma IL-6 was associated with significantly faster atrophy rates (yellow = areas of statistical significance after threshold using posterior probability maps and p<.05 alpha). We did not observe associations of baseline plasma IL-6 and brain volume cross-sectionally at baseline using voxel-based morphometry analyses, and plasma IL-6 did not relate significantly to clinical outcomes in this sample.
**Supplemental Figure 7**: Baseline TNFα associations with longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) stratified by each pathogenic variant group. Longitudinal trend lines are shown for participants with low (<25th percentile, green line) or high (>75th percentile, blue line) plasma TNFα concentrations. Statistically significant associations (* = p < .05) indicate where high baseline plasma TNFα was associated with more rapid clinical decline. Analyses that further incorporated non-carrier family members showed that each of these significant relationships also were specific to the pathogenic variant carriers.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score
Supplemental Figure 8: Baseline IL-6 associations with longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) stratified by each pathogenic variant group. Longitudinal trend lines are shown for participants with low (<25th percentile, green line) or high (>75th percentile, blue line) plasma IL-6 concentrations. Statistically significant associations (* = p < .05) indicate where high baseline plasma IL-6 was associated with more rapid clinical decline. Analyses that further incorporated non-carrier family members showed that the significant relationship was specific to the pathogenic variant carriers.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score
Supplemental Figure 9: Baseline YKL-40 associations with longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) stratified by each pathogenic variant group. Longitudinal trend lines are shown for participants with low (<25<sup>th</sup> percentile, green line) or high (>75<sup>th</sup> percentile, blue line) plasma YKL-40 concentrations. Statistically significant associations (* = p < .05) indicate where high baseline plasma YKL-40 was associated with more rapid clinical decline. Analyses that further incorporated non-carrier family members showed that the significant relationships were specific to the pathogenic variant carriers.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score
SUPPLEMENTAL MATERIAL

Supplemental Methods

Participants

The study included 394 participants in the ALLFTD consortium. ALLFTD represents a harmonized merger of two complementary familial FTLD studies initiated in 2014: The Advancing Research and Treatment of Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFTTDS) studies. The ALLFTD consortium currently includes 23 centers across the United States and Canada (allftd.org) with 18 contributing data to this project. Sites enroll individuals based on a family history suggestive of familial FTLD, usually identified through interview of a symptomatic proband. Once a family member with a pathogenic variant is identified, other members of the family are contacted and invited to participate. Enrollees do not need to know their genetic status. Only patients with pathogenic C9orf72, GRN, or MAPT variants, or non-carrier family members, were included in the analyses reported here. Genetic screening for the three major autosomal dominant pathogenic variants plus apolipoprotein E genotyping methods are described in detail elsewhere[1].

The 394 study participants included 251 FTLD pathogenic variant carriers (C9orf72=117, GRN=62, MAPT=72) and 143 functionally normal, non-carrier family members with at least one of the three inflammation proteins (IL-6, YKL-40, TNFα) analyzed at baseline. 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 vs. Non-converters

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

Plasma Collection and Protein Measurement

Blood samples were collected and stored following standardized procedures for the ALLFTD consortium. Plasma IL-6, YKL-40, and TNFα concentrations were quantified using Meso Scale Discovery (MSD) chemiluminescence assays. IL-6 and TNFα were measured via automated multiplex (UCSF Gladstone Institute; completed June 2019) and selected from the larger set of markers for the present study given their broad relevance within systemic inflammatory pathways and both analytes were consistently quantified in the linear range of detection. YKL-40 was measured via singleplex (San Francisco VA hospital core lab; completed December 2019). All samples underwent two freeze thaw cycles during the analyte measurement process. Batch effects were minimized through sample randomization by the National Centralized
Repository for Alzheimer’s Disease and Related Dementias (NCRAD) prior to shipment to UCSF.

All 394 participants had at least one inflammatory biomarker measured (IL-6, N=375; YKL-40, N=394; TNFα, N=389). Samples with coefficient of variation (CV%) >25% were excluded from all analyses (IL-6, N=35; YKL-40, N=0; TNFα, N=21). After exclusion of samples with high CV%, mean±SD CV% were 8.7±6.4% (IL-6), 1.8±1.8% (YKL-40), and 8.7±4.6% (TNFα).

Through a separate study, plasma NfL concentrations were measured with single-molecule array technology (Simoa) using the commercially available NF-light digital immunoassay kit (Quanterix, Lexington, MA), as described elsewhere[3]. Plasma samples were thawed at room temperature (1 cycle), mixed thoroughly, and centrifuged at 14,000g for 3 minutes. The supernatant was loaded onto a Quanterix HD-1 Analyzer with 1:4 specified dilution. Samples were measured in duplicate with an 8-point calibration curve tested in triplicate and 2 controls tested in duplicate. Plasma concentrations were interpolated from the calibration curve within the same batch and corrected for the dilution. All samples were quantifiable within the dynamic range of 0.69-2,000 pg/mL with average coefficient of variation of 6.2±4.3%. The samples from the subset of participants with plasma NfL data included in this study all had CV<20%.

Functional, Behavioral, and Cognitive Assessments

Primary Clinical Outcome: Clinical Disease Severity

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 optimized for FTD spectrum cohorts[2, 4]. It can be used to generate a “Global” score that represents a weighted average of eight functional domain scores to categorize each patient as asymptomatic (CDR+NACC FTLD Global=0), prodromal mild cognitive or behavioral symptoms of neurodegenerative disease[4] ("prodromal"; CDR+NACC FTLD Global =0.5), or clear functionally impairing symptoms consistent with dementia ("overtly symptomatic:" CDR+NACC FTLD Global >1). For analyzing longitudinal clinical disease severity, we used the CDR+NACC FTLD Sum of Boxes (SB) score (range 0 to 24; higher scores indicate worse severity).

Secondary Clinical Outcomes: Socioemotional Sensitivity and Cognition

We evaluated longitudinal changes in socioemotional sensitivity using the Revised Self-Monitoring Scale (RSMS) total score[5]. The RSMS is a validated 13-item questionnaire that measures sensitivity and responsiveness to subtle emotional expressions during face-to-face interactions. The questionnaire has good internal consistency, retest reliability, and construct validity[6, 7]. The RSMS was completed by an informant who was a first-degree family member or friend who had known the participant for ≥5 years. Informants rated patients on each item on a 6-point Likert scale ranging from “certainly, always false” to “certainly, always true,” with lower scores representing more severe dysfunction (i.e., less socioemotional sensitivity). The RSMS has been shown to be sensitive to progression of both socioemotional symptoms and salience network atrophy in patients with familial and non-familial forms of the behavioral variant phenotype of FTLD[8, 9]. Behavioral variant phenotypes are the most common symptom presentation in the ALLFTD cohort.

We defined cognition using the National Alzheimer's Coordinating Center Uniform Data Set (v3.0) executive function composite score (UDS3-EF)[10]. The UDS3-EF is an item response
theory-based composite derived from 7 total UDS3-EF test scores: category fluency (animals and vegetables; total correct), lexical fluency (F and L words; total correct), number span backward (total correct trials), Trail Making Test parts A and B (correct lines per minute). The cognitive domains that factor into the UDS3-EF score (e.g., mental set-shifting, verbal fluency, attention/working memory) support the potential utility as a single composite measure of the common cognitive changes observed across a range of clinical phenotypes in FTLD spectrum patients. Higher UDS3-EF scores suggest better executive functioning, and a validation study showed significantly lower scores in bvFTD patients compared to controls and other patient groups[10]. Additionally, the Montreal Cognitive assessment (MoCA) was analyzed to help characterize global cognition in the study cohort at baseline.

**Voxel-Based Morphometry**

Volumetric MPRAGE sequences acquire T1-weighted images of the entire brain (sagittal slice orientation; slice thickness = 1.2 mm; in-plane resolution = 1.0x1.0 mm; TR, TE and flip angle are vendor specific according to the LEFFTDS recommendation[11]. Before any prepossessing of the images, all T1-weighted images were visually inspected for quality control. Images with excessive motion or image artifact were excluded. T1-weighted images underwent bias field correction using N3 algorithm, and segmentation was performed using SPM12 (Wellcome Trust Center for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm) unified segmentation[12]. An intra-subject template was created by non-linear diffeomorphic and rigid-body registration proposed by the symmetric diffeomorphic registration for longitudinal MRI framework[13]. The intra-subject template was segmented also using SPM12's unified segmentation. A within-subject modulation was applied by multiplying the timepoints' Jacobian determinant with the intra-subject averaged tissues[14]. A customized group template was generated from the within-subject average gray and white matter tissues and cerebrospinal fluid by non-linear registration template generation using Large Deformation Diffeomorphic Metric Mapping framework[15]. Modulated intra-subject gray and white matter were geometrically normalized to the group template and then smoothed using approximately 8mm full width half maximum Gaussian kernel in the group template. Every step of the transformation was carefully inspected from the native space to the group template. For statistical purposes, linear and non-linear transformations between the group template space and International Consortium of Brain Mapping (ICBM) were applied[16]. For the cross-sectional analysis, the baseline time points were modulated by taking the determinant of the Jacobian composed transformations from the native space to the group template. We used the same smoothing kernel as previously described.

**Data Analyses**

Analyses were performed using SPSS (IBM Corporation; Versions 25.0 and 27.0). Group differences in potentially confounding variables (age, sex, education) between pathogenic variant carriers and non-carriers were analyzed with linear regression models. We further assessed differences in global cognition (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. We evaluated histograms and Q-Q plots of residuals for all regression models. Dependent variables were log transformed when there were clear departures from normality.

**Cross-sectional Group Comparisons**
We performed linear regressions to evaluate baseline plasma inflammation differences between pathogenic variant carriers and non-carriers and between the three genetic groups (dummy coded to interpret pairwise genetic group differences) controlling for age, sex, and years of education. To determine whether presence of a pathogenic variant (versus 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 also compared inflammatory protein levels among genetic groups (C9orf72 vs. GRN vs. MAPT) while additionally controlling for disease severity (CDR+NACC FTLD SB).

We then specifically 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+). Effect sizes were interpreted based on standardized beta (β) estimates: 0.1 = small, 0.3 = medium, 0.5 = large.

**Baseline Inflammation and Rate of Functional, Socioemotional, and Cognitive Changes**

We used linear mixed effects models (restricted maximum likelihood estimation) with random slopes and intercepts (unstructured covariance) to evaluate the association between baseline inflammation levels and longitudinal changes in our primary (CDR+NACC FTLD SB) and secondary (RSMS total score, UDS3-EF score) clinical outcomes. Each participant's baseline was defined as the first study visit with an available plasma inflammation biomarker measurement. Longitudinal models excluded pathogenic variant carriers with baseline CDR+NACC FTLD Global>1 to limit ceiling effects associated with severe impairment at baseline.

Our primary goal was to determine whether baseline inflammation levels were associated with rates of change in clinical outcomes among pathogenic variant carriers. We therefore evaluated the interaction between baseline inflammation level and time since baseline visit and present unstandardized regression estimates controlling for baseline age, sex, and years of education among known pathogenic variant carriers. Each genetic group was analyzed in separate models and interpreted using Benjamini-Hochberg adjusted alpha levels (false discovery rate p<.05)[17].

Secondarily, we 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 significant three-way interaction would indicate that the association between baseline inflammation and longitudinal clinical outcomes observed in pathogenic variant carriers was significantly stronger (or weaker) than the effect of baseline inflammation observed in non-carriers. These analyses were only performed when a significant association between baseline inflammation and longitudinal clinical outcomes was first observed among pathogenic variant carriers.

**Neuroimaging Analyses**

The image analyses were conducted using FSL[18] for the voxel based morphometry cross sectional analysis. The familywise error correction was performed using 5000 permutations with threshold free cluster enhancement[19]. The effect, at baseline, of the inflammation markers was corrected for age, gender and total intracranial volume. The longitudinal analyses were performed in the Bayesian linear mixed-effect model framework[14]. The interaction between
rate of change and inflammation marker at baseline was threshold using the posterior probability maps with an alpha = 5%. Neuroimaging analyses were restricted to pathogenic variant carriers and stratified by gene group given regional atrophy pattern differences expected between groups[20-22].

**Identifying Asymptomatic Converter Pathogenic Variant Carriers**

Among pathogenic variant carriers, we compared plasma inflammatory markers between asymptomatic non-converters and asymptomatic converters. Inflammatory proteins that significantly differed were then evaluated using area under the receiver operating characteristic curve analyses (AUC/ROC) in the same participants to further inform the clinical relevance of observed group-level associations. These analyses were repeated in a subset of participants who also had plasma NfL levels measured previously. Binary logistic regression models 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[3, 23].

Supplemental Results

Descriptive Comparisons and Baseline Differences

Pathogenic variant carriers were older than non-carriers. There were no statistically significant differences in the proportion of female participants, years of education, or frequency of apolipoprotein E e4 carriers between carriers and noncarriers. As expected, pathogenic variant carriers had significantly lower MoCA total score, higher CDR+NACC FTLD SB, lower RSMS total score, and lower UDS3-EF score than non-carriers. Within pathogenic variant carriers, age differed between genetic groups (\textit{GRN} > \textit{C9orf72} > \textit{MAPT}). There were no statistically significant differences across genotypes in proportion of female participants, years of education, apolipoprotein E e4 carrier frequency, MoCA total score, CDR+NACC FTLD SB, RSMS total score, or proportion of symptomatic participants at baseline (CDR+NACC FTLD Global>0). \textit{C9orf72} carriers had lower baseline UDS3-EF scores than \textit{MAPT} carriers (p=.04).

Cross-Sectional Group Comparisons of Plasma Inflammation Levels

Asymptomatic non-converter pathogenic variant carriers had significantly lower baseline levels of plasma TNFα (β=-.16 [-.31, -.02], p=.03) and IL-6 (β=-.21 [-.34, -.06], p=.006) than non-carrier family members (data not shown). Among all pathogenic variant carriers at baseline, \textit{MAPT} carriers had higher levels of IL-6 than \textit{C9orf72} (β=.17 [.01, .32], p=.03) and \textit{GRN} carriers (β=.16 [.001, .33], p=.048).

Among pathogenic variant carriers, baseline inflammation levels differed based on clinical disease severity (Supplemental Figure 1). Prodromal carriers (CDR+NACC FTLD Global=0.5) had statistically significantly higher plasma TNFα levels than asymptomatic carriers (β=.16 [.02, .30], p=.02). Pathogenic variant carriers with dementia (CDR+NACC FTLD Global ≥ 1) had higher plasma IL-6 than asymptomatic carriers (β=.22 [.06, .37], p=.006).
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Supplemental Table 1: Number of participants with all three plasma inflammatory markers measured and eligible for analyses (N=334; 85% of total sample with at least one inflammatory marker). Across non-carrier kindred and pathogenic variant carriers, 120/143 (84%) of non-carrier kindred and 214/251 (85%) of pathogenic variant carriers had all three inflammatory markers. Refer to Table 1 for frequency of participants with at least one available inflammatory markers across individual clinical phenotypes (Clinically Normal, bvFTD, MBI, etc.).
Supplemental Figure 1: Comparison of baseline plasma inflammatory proteins among pathogenic FTLD gene variant carriers. Prodromal participants (CDR+NACC FTLD Global score = 0.5) had significantly higher plasma TNFα than asymptomatic participants (CDR+NACC FTLD Global score = 0). For plasma IL-6, overtly symptomatic participants (CDR+NACC FTLD Global score > 1.0) had significantly higher concentrations than asymptomatic participants. No group differences in plasma YKL-40 were observed between asymptomatic, prodromal, and overtly symptomatic participants. Separate box-and-whisker plots are shown for each gene group for visualization only. Gene groups were combined for analyses.
Supplemental Figure 2: Inter-correlations between plasma inflammatory markers and their association with participant age (baseline). (A) All associations between plasma inflammatory markers at baseline were statistically significant (p < .03) with small to moderate effect sizes. (B) All associations between plasma inflammatory markers and participant age were statistically significant (p < .001) and ranged from small (.17, TNFα) to relatively large (.47, YKL-40) effect sizes. These relationships were similar or slightly stronger when restricting only to pathogenic variant carriers.
**Supplemental Figure 3:** Associations between baseline plasma inflammatory marker concentrations and longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) for pathogenic variant carriers (all gene groups combined). Longitudinal trend lines are shown for participants with low (<25th percentile, green line) or high (>75th percentile, blue line) inflammatory marker concentrations for each of the three markers evaluated (TNFα, IL-6, YKL-40). Statistically significant associations (* = p < .05) indicate where high baseline plasma inflammation was associated with more rapid clinical decline.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score
Supplemental figure 4: Multi-slice axial views showing the association of baseline plasma TNFα concentrations with brain volume among pathogenic MAPT variant carriers. (A) At baseline (cross-sectionally), voxel-based morphometry analysis revealed that higher TNFα was associated with lower brain volume in a small region of the left anterior temporal lobe (orange = p<.05 after family-wise error correction using 5,000 permutations with threshold-free cluster enhancement). (B) Longitudinally, Bayesian linear mixed-effects (BLME) analyses revealed widespread areas where higher baseline plasma TNF-alpha was associated with significantly faster atrophy rates (warmer colors = steeper atrophy slopes; threshold using posterior probability maps and p<.05 alpha). These multi-slice images correspond with the selected representative slices presented in main Figure 1.
Supplemental figure 5: Multi-slice axial views showing the association of baseline plasma IL-6 concentrations with brain volume among pathogenic C9orf72 variant carriers. 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 (red = p<.10 after family-wise error correction using 5,000 permutations with threshold-free cluster enhancement). There was no significant association of baseline plasma IL-6 concentrations with the rates of brain atrophy longitudinally. These multi-slice images correspond with the representative slices presented in main Figure 2.
**Supplemental figure 6**: Multi-slice axial views showing the association of baseline plasma IL-6 concentrations with brain volume among pathogenic GRN variant carriers. Longitudinally, Bayesian linear mixed-effects (BLME) analyses revealed scattered areas in subcortical, temporal, insula, and dorsal parietal/precuneus regions where higher baseline plasma IL-6 was associated with significantly faster atrophy rates (yellow = areas of statistical significance after threshold using posterior probability maps and p<.05 alpha). We did not observe associations of baseline plasma IL-6 and brain volume cross-sectionally at baseline using voxel-based morphometry analyses, and plasma IL-6 did not relate significantly to clinical outcomes in this sample.
Supplemental Figure 7: Baseline TNFα associations with longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) stratified by each pathogenic variant group. Longitudinal trend lines are shown for participants with low (<25th percentile, green line) or high (>75th percentile, blue line) plasma TNFα concentrations. Statistically significant associations (* = p < .05) indicate where high baseline plasma TNFα was associated with more rapid clinical decline. Analyses that further incorporated non-carrier family members showed that each of these significant relationships also were specific to the pathogenic variant carriers.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score
Supplemental Figure 8: Baseline IL-6 associations with longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) stratified by each pathogenic variant group. Longitudinal trend lines are shown for participants with low (<25th percentile, green line) or high (>75th percentile, blue line) plasma IL-6 concentrations. Statistically significant associations (* = p < .05) indicate where high baseline plasma IL-6 was associated with more rapid clinical decline. Analyses that further incorporated non-carrier family members showed that the significant relationship was specific to the pathogenic variant carriers.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score.
Supplemental Figure 9: Baseline YKL-40 associations with longitudinal clinical outcomes (CDR+NACC FTLD Sum of Boxes, RSMS total score, UDS3-EF score) stratified by each pathogenic variant group. Longitudinal trend lines are shown for participants with low (<25th percentile, green line) or high (≥75th percentile, blue line) plasma YKL-40 concentrations. Statistically significant associations (* = p < .05) indicate where high baseline plasma YKL-40 was associated with more rapid clinical decline. Analyses that further incorporated non-carrier family members showed that the significant relationships were specific to the pathogenic variant carriers.

CDR+NACC FTLD SB = Clinical Dementia Rating plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration module Sum of Boxes, RSMS = Revised Self-Monitoring Scale, UDS3-EF = Uniform Data Set version 3 Executive Function composite score