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Full-length Article

Inflammatory plasma profile in genetic symptomatic and presymptomatic Frontotemporal Dementia – A GENFI study

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ABSTRACT

Background: Inflammation has been proposed as a crucial player in neurodegeneration, including Frontotemporal Dementia (FTD). A few studies on sporadic FTD lead to inconclusive results, whereas large studies on genetic FTD are lacking. The aim of this study is to determine cytokine and chemokine plasma circulating levels in a large cohort of genetic FTD, collected within the GENetic Frontotemporal dementia Initiative (GENFI).
Methods: Mesoscale technology was used to analyse levels of 30 inflammatory factors in 434 plasma samples, including 94 Symptomatic Mutation carriers [(SMC); 15 with mutations in Microtubule Associated Protein Tau (*MAPT*) 34 in Progranulin (*GRN*) and 45 in Chromosome 9 Open Reading Frame (*C9ORF)72*], 168 Presymptomatic Mutation Carriers (PMC; 34 *MAPT*, 70 *GRN* and 64 *C9ORF72*) and 173 Non-carrier Controls (NC)].
Results: The following cytokines were significantly upregulated ($P<0.05$) in *MAPT* and *GRN* SMC versus NC: Tumor Necrosis Factor (TNF)α, Interleukin (IL)-7, IL-15, IL-16, IL-17A. Moreover, only in *GRN* SMC, additional factors were upregulated, including: IL-1β, IL-6, IL-10, IL-12/IL-23p40, eotaxin, eotaxin-3, Interferon γ-induced Protein (IP-10), Monocyte Chemotactic Protein (MCP)4. On the contrary, IL-1α levels were decreased in SMC compared with NC. Significantly decreased levels of this cytokine were also found in PMC, independent of the type of mutation. In SMC, no correlations between disease duration and cytokine and chemokine levels were found.
Considering NfL and GFAP levels, as expected, significant increases were observed in SMC as compared to NC. These differences in mean values remain significant even when stratifying symptomatic patients by the mutated gene ($P<0.0001$).
Considering instead the levels of NfL, GFAP, and the altered inflammatory molecules, no significant correlations emerged.
Conclusion: We showed that inflammatory proteins are upregulated in *MAPT* and *GRN* SMC, with some specific factors altered in *GRN* only, whereas no changes were seen in *C9ORF72* carriers. Notably, only IL-1α levels were decreased in both SMC and PMC, independent of the type of causal mutation, suggesting common modifications occurring in the preclinical phase of the disease.

1. Introduction

Frontotemporal dementia (FTD) encompasses various clinical syndromes. The most common is the behavioural variant (bv)FTD, characterized by the presence of behavioral disturbances, aggressiveness, lack of empathy and decline in social conduct, followed by non-fluent variant Primary Progressive Aphasia (nfvPPA) and semantic variant (sv)PPA. About 50 % of FTD cases show a family history for dementia, often with dominant traits (Pottier et al., 2016). At the pathological level, all syndromes described are collectively grouped as Frontotemporal Lobar Degeneration (FTLD). At histopathology, based on the type of protein depositing, FTLD is classified into FTLD-Tau, FTLD-TAR DNA Binding protein (TDP)43, and FTLD fused in Sarcoma (FUS) (Rademakers et al., 2012). Three major causal genes responsible for autosomal dominant inherited FTD have been discovered so far, including microtubule associated protein tau (*MAPT*), characterized by deposition of tau protein in the brain, progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9ORF72*), both characterized by deposition of TDP-43. *MAPT* carriers quite often develop bvFTD and parkinsonism, whereas *GRN* mutations are associated with phenotypic heterogeneity, including the classical syndromes but also atypical presentations such as Corticobasal syndrome (CBS) and Progressive Supranuclear Palsy (PSP) (Swift et al., 2024). The *C9ORF72* expansion instead may present not only with FTD but also with Amyotrophic Lateral Sclerosis (ALS), or both, and is often associated with late onset psychosis (Galimberti et al., 2013).

As regards downstream pathogenic mechanisms leading to symptom development, inflammation has been found to be involved in FTD far before the discovery of *GRN* and *C9ORF72* mutations (Galimberti et al., 2006). More recent studies compared genetic with sporadic cases. In 2015, a study on cerebrospinal fluid (CSF) demonstrated that *GRN* carriers display a specific CSF signature as compared with sporadic FTD (Galimberti et al., 2015). More recently, it has been shown that a few free circulating microRNAs and long non-coding RNAs, which could regulate cytokine and chemokine expression, are decreased in *GRN* and *C9ORF72* carriers (Fenoglio et al., 2022). In this scenario, progranulin (PGRN) is an intriguing player: it is involved in processes ranging from tumorigenesis and inflammation to neural proliferation (Huang et al., 2023) and, in FTD caused by *GRN* haploinsufficiency mutations, deficits in PGRN lead to pathological processes, including TDP-43 accumulation, lysosomal dysfunction, complement activation, neuroinflammation, and astrogliosis (Boylan et al., 2023). Moreover, the absence of PGRN causes alterations in microglial phenotypes, leading to an increase in lysosomal dysfunction and neuroinflammation, heightened production of complement proteins, and intensified synaptic pruning (Lui et al., 2016). Mutations in *MAPT* cause hyperphosphorylation of tau protein due to an imbalance in protein phosphatase 2A (PP2A) and glycogen synthase kinase-3 beta (GSK-3β); in this context, experimental evidence suggests that inhibition of PP2A and increased GSK-3β activity contribute to neuroinflammation, oxidative stress, and cognitive impairment (Manoharan et al., 2024). Regarding the *C9ORF72* gene, although its exact function remains unknown, there is evidence suggesting that

[1] Chiara Fenoglio and Maria Serpente shared first authorship.
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neuroinflammation may play a role in C9-ALS/FTD. C9-ALS/FTD refers to the overlap between ALS and FTD caused by mutations in the *C9ORF72* gene, which is the most common genetic cause of both disorders. Patients with these mutations often exhibit symptoms of both ALS, characterized by motor neuron degeneration, and FTD, characterized by cognitive and behavioral impairments.

The exact role of neuroinflammation in neurodegeneration remains debated, as immune system dysregulation is a pathological hallmark in nearly all neurodegenerative diseases (Masrori et al., 2022). Specifically, studies have shown that patients with *C9ORF72* mutations exhibit elevated levels of inflammatory markers, which suggests a possible contribution of neuroinflammation to disease progression. For instance, elevated levels of cytokines such as IL-6 and TNF-α have been observed in patients with C9-ALS/FTD, indicating an ongoing inflammatory response (Masrori et al., 2022)."

Here, we show results of a plasma profiling study of inflammatory factors (cytokines and chemokines) in the very well characterized genetic GENetic Frontotemporal dementia Initiative (GENFI) cohort. To our knowledge, a large study of these molecules has not been done yet in genetic FTD, which represent the best model of the disease as the pathology can be predicted in life.

2. Materials and methods

2.1. Population

All demographic and clinical data, as well as samples included in the study, were collected within the GENFI, a natural history study of genetic FTD involving 23 research centres across Europe and Canada (https://www.genfi.org.uk) (Rohrer et al., 2015). Variables included were: age at sampling, age at onset, sex, mutation group (symptomatic mutation carriers, SMC; presymptomatic mutation carriers, PMC; non-carrier family members considered as controls, NC), mutated gene (*MAPT*, *GRN*, *C9ORF72*), clinical phenotype. Four hundred thirty-five plasma samples were collected, including 94 SMC (15 *MAPT*, 34 *GRN* and 45 *C9ORF72*; mean age at onset years ± SD: 62 ± 11, 69 ± 11 and 63 ± 9, respectively), 168 PMC (34 *MAPT*, 70 *GRN* and 64 *C9ORF72*) and 173 NC. Carriers of other rare FTD causing mutations were not included. Demographics of the population are shown in Table 1. Diagnoses of patients were as follows: 64 with bvFTD, 17 PPA, 6 ALS, 5 bvFTD/ALS, 1 CBS, 1 symptoms non meeting any of the above. The GENFI study was performed in accordance with the Declaration of Helsinki, reviewed and approved by all countries' respective Ethics Committees and all participants signed an informed consent to take part in the research. This research study was performed in Italy, Ethics Committee Milano Area 2, parere 882_2022 del 13–9-22.

2.2. Sample processing

Blood samples (n = 435) were collected at 20 different sites in Europe and Canada in ethylenediaminetetraacetic acid (EDTA) tubes. Samples were centrifuged at room temperature and the supernatant plasma was transferred to polypropylene cryotubes and stored at −80C° until analysis.

Table 1
Characteristics of study groups.

	Non Carriers (NC)	Presymptomatic Mutation Carriers (PMC)	Symptomatic Mutation Carriers (SMC)
Subjects (n)	173	168	94
Age, mean years (SD)	47 (12)	44 (12)	65 (7)
Gender distribution, females:males	106:67	116:52	40:54
NfL pg/ml (SEM)	9.75 (0.78)	14,10 (2.20)	59.05 (5.91)*
GFAP pg/ml (SEM)	106.20 (12)	102,20 (6.10)	186.30 (10.26)*

*$P<0.0001$ vs NC and PMC.

2.3. Mesoscale

Inflammatory molecules were measured on the V-Plex Meso Scale Discovery (MSD) electrochemiluminescence multi-spot assay platform (MesoScale Diagnostics). Plasma samples were measured in duplicate using 25 uL of undiluted plasma per replicate.

Plasma was used for the V-Plex Chemokine Panel 1 [Eotaxin, Eotaxin-3, TARC, interferon γ-induced protein 10 kDa (IP10), Macrophage Inflammatory Protein (MIP)1α, MIP1β, Interleukin (IL)8, Monocyte Chemotactic Protein (MCP)1, Macrophage Derived Chemokine (MDC) and MCP4], Cytokine Panel 1 [Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), IL1α, IL5, IL7, IL12/IL23p40, IL15, IL16, IL17A, Tumor Necrosis Factor (TNF)β, Vascular Endothelial Growth Factor (VEGF)-A] and Proinflammatory Panel 1 [Interferon (IFN)γ, IL1β, IL2, IL4, IL6, IL8, IL10, IL12p70, IL13, TNFα]. Each plate was read on a Meso Quickplex SQ120 with absolute target protein levels (pg/ml) obtained and normalized to the total protein amount. Data were analysed with the MSD discovery workbench tool.

2.4. Plasma neurofilament light chain (NfL) and Glial Fibrillary Acidic protein (GFAP)

Plasma neurofilament light chain (NfL) and Glial Fibrillary Acidic Protein (GFAP) levels were measured on the SIMOA HD-1 analyzer, as previously described (Heller et al., 2020).

2.5. Statistical analysis

Statistical analysis was performed using GraphPad Prism V9.0 (GraphPad Software, San Diego, USA). Normality was tested with the Kolmogorov Smirnov's test. Comparisons between study groups and controls were performed using Kruskal-Wallis test and data were adjusted for multiple comparison by using the Dunn's post hoc test. Correlations between the different proteins within each study group was assessed with Pearson's or Spearman's test depending on normality. To account for multiple testing, the Benjamini, Krieger and Yekutieli procedure to control for the false discovery rate (FDR) was used as post hoc correction. Adjusted P-values < 0.05 for intergroup comparisons and 0.01 for correlations were considered significant.

3. Results

A pattern of mainly upregulated inflammatory factors was observed in SMC with *MAPT* and *GRN* mutations, whereas no significant changes were observed in those carrying the *C9ORF72* expansion. Mean values (pg/ml ± SEM) are summarized in the Supplementary Table.

In detail, the following cytokines (pg/ml ± SEM) were significantly upregulated in *MAPT* and *GRN* SMC versus NC, respectively: TNF α (3.23 ± 0.75 and 3.25 ± 0.47 versus 1.27 ± 0.09, $P<0.0001$), IL-7 (18.68 ± 2.22 and 14.46 ± 1.18 versus 9.65 ± 0.81, $P<0.001$ and 0.05), IL-15 (2.90 ± 0.27 and 2.12 ± 0.2 versus 1.30 ± 0.11, $P<0.0001$ and 0.001), IL-16 (217.40 ± 19.52 and 241.50 ± 17.66 versus 135.70 ± 11.35, $P<0.05$ and 0.0001), IL-17A (5.37 ± 0.86 and 6.19 ± 1.95 versus 5.75 ± 1.75, $P<0.05$ and 0.001; Fig. 1). Moreover, only in *GRN* SMC, additional cytokines and chemokines were upregulated, including: IL-1 α (0.16 ± 0.03 versus 0.05 ± 0.01, $P<0.001$), IL-6 (1.28 ± 0.26 versus 0.71 ± 0.11, $P<0.001$), IL-10 (0.32 ± 0.03 versus 0.19 ± 0.03, $P<0.0005$), IL-12/IL-23p40 (105.40 ± 12.78 versus 78.11 ± 21.29, $P<0.001$), eotaxin (387.90 ± 28.36 versus 256.00 ± 16.48, $P<0.001$), eotaxin-3 (27.57 ± 3.50 versus 15.44 ± 1.60, $P<0.05$), IP-10 (365.70 ± 30.03 versus 260.80 ± 21.82, $P<0.001$), MCP4 (182.40 ± 15.02 versus

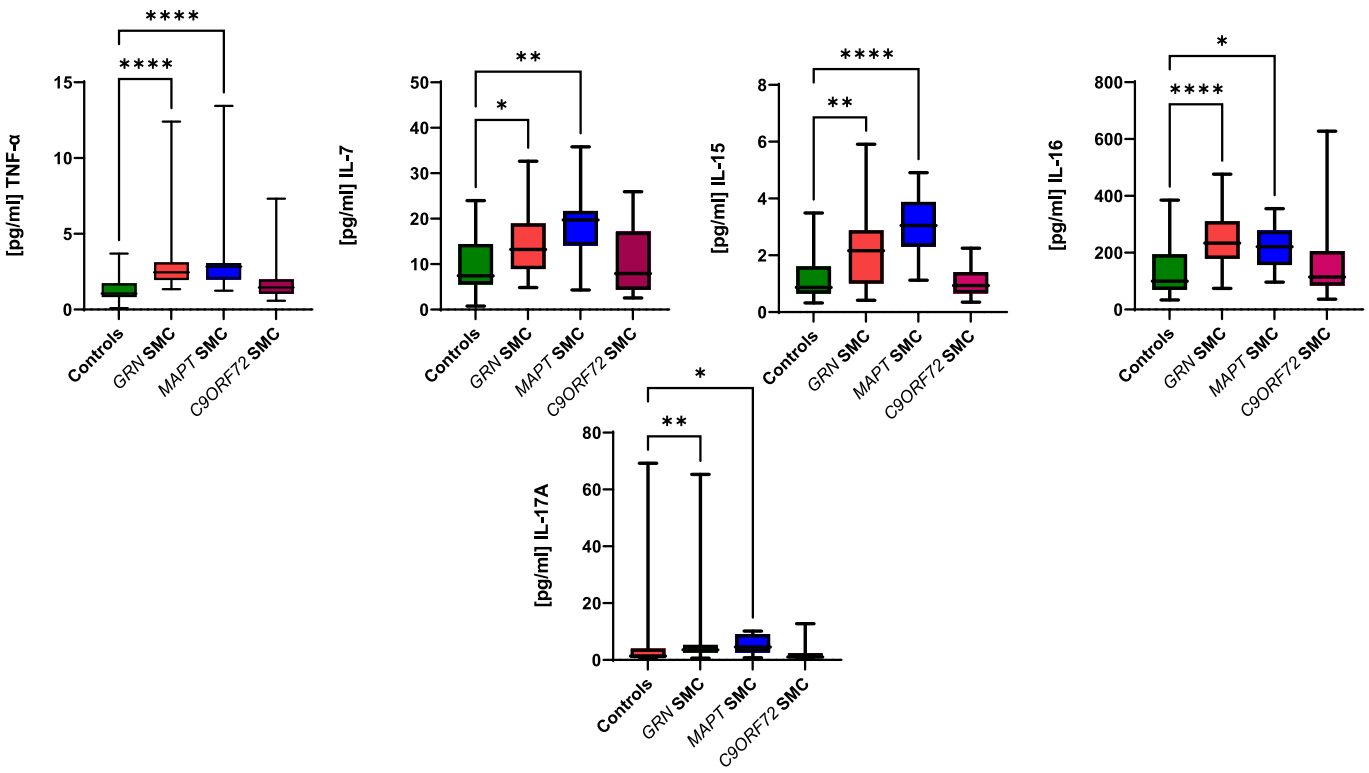

Fig. 1. Box and whisker plots showing inflammatory factors up-regulated in *GRN* and *MAPT* SMC. *P<0.05. **P<0.001. ****P<0.0001.

128.50 ± 128.50, P<0.05; Fig. 2). No significant differences were shown in PMC versus NC (P>0.05).

On the contrary, IL-1α levels (pg/ml ± SEM) were decreased in SMC compared with NC. Notably, this decrease was statistically significant for carriers of *GRN* and *C9ORF72* mutations (4.27 ± 1.14 and 1.53 ± 0.43 versus 12.19 ± 2.36, P<0.001 and 0.05; Fig. 3), while it was inconclusive for carriers of mutations in *MAPT* gene as in 60 % of samples levels were below the detection threshold (in the detectable

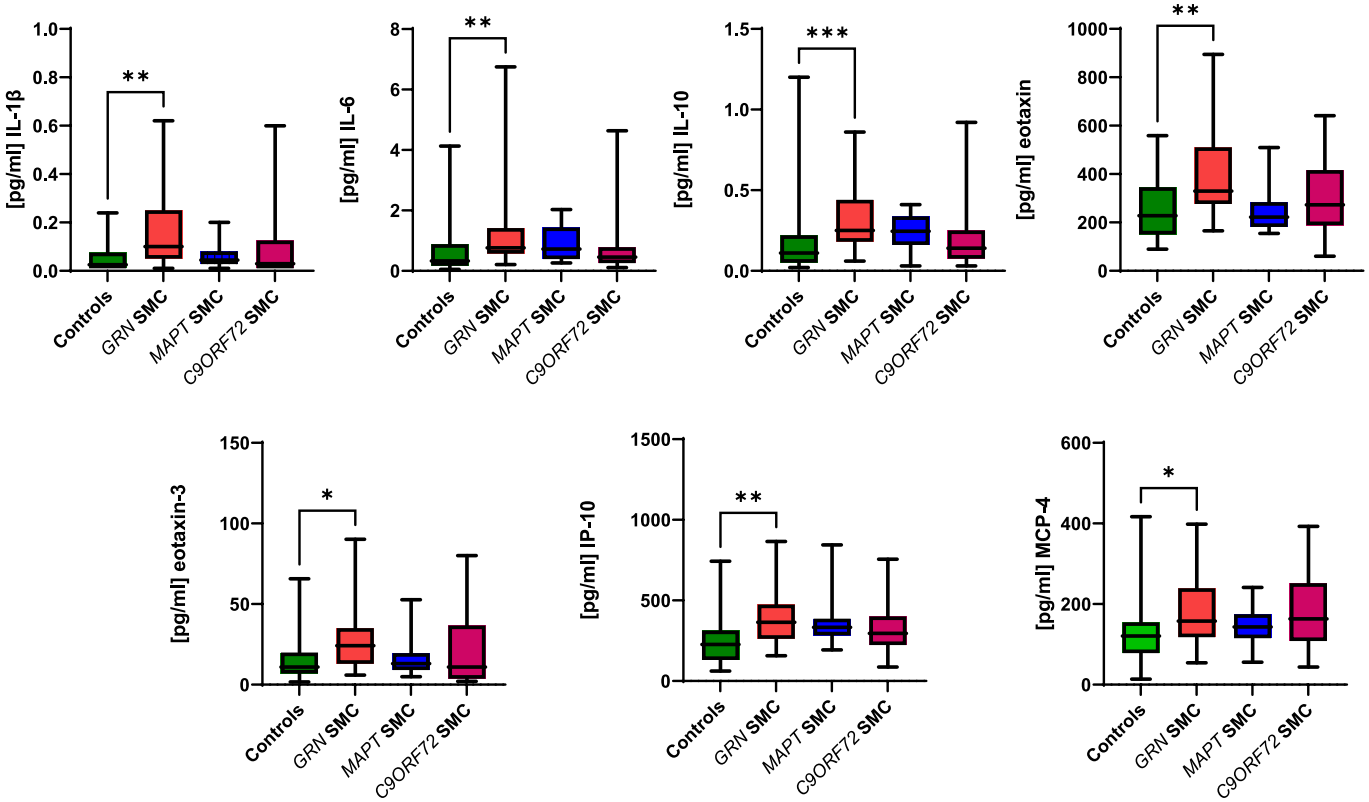

Fig. 2. Box and whisker plots showing inflammatory factors up-regulated in *GRN* SMC. *P<0.05. **P<0.001. ***P<0.0005.

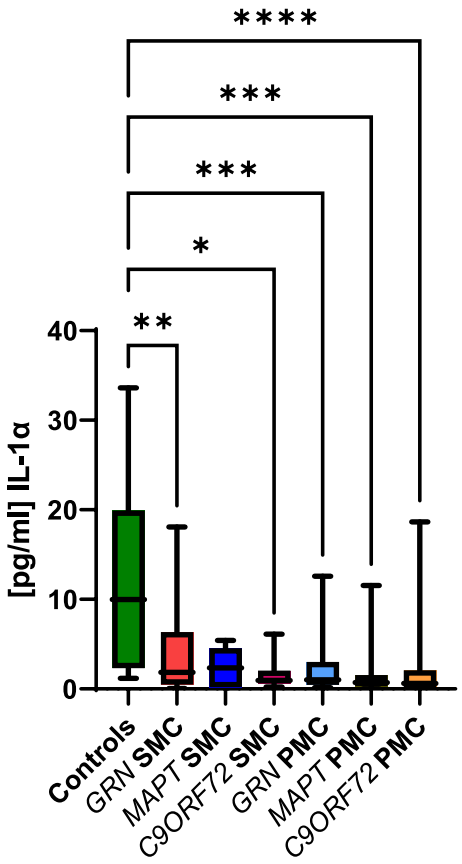

Fig. 3. Box and whisker plot showing IL-1α down-regulation in SMC and PMC. *$P<0.05$. **$P<0.001$. ***$P<0.0005$. ****$P<0.0001$.

samples: 2.45 ± 0.86 versus 12.19 ± 2.36, $P>0.05$). Similar significantly decreased levels of this cytokine were also found in PMC versus NC, independent of the type of mutation (Fig. 3).

As PMC group included individuals with a very wide range of age, we correlated IL-1α with the difference between the age at sampling and the mean familial age at onset to estimate time to expected symptoms, but found no significant correlations.

Stratifying by gender, a few significant differences were observed. In particular, in *GRN* and *MAPT* SMC, IL-15 levels were significantly increased in males as compared with male NC (*GRN*: 2.28 ± 0.39 pg/ml and *MAPT*: 3.26 ± 0.46 versus 1.09 ± 0.17 pg/ml; $P=0.02$ and $P=0.0006$ respectively), while they do not differ significantly in female SMC compared with gender matched NC (Supplementary Figure, panel A). Conversely, considering IL-17A, we observed that levels were significantly increased only in female SMC of *GRN* and *MAPT* mutations versus NC (*GRN*: 4.27 ± 0.52 pg/ml and *MAPT*:6.48 ± 1.2 pg/ml versus 1.99 ± 0.34 pg/ml respectively, $P<0.006$, Supplementary Figure, panel A). In *GRN* SMC, we observed that stratifying by gender, IL-6 levels remain significantly increased only in females (1.24 ± 0.76 pg/ml versus female NC 0.76 ± 0.16 pg/ml, $P=0.04$), whereas IP-10 levels remained significantly increased only in males (407.4 ± 42.9 pg/ml versus 237.4 ± 30.5 pg/ml, $P=0.01$, Supplementary Figure, panel B).

No correlations between disease duration in symptomatic individuals and cytokine and chemokine levels was found. Main functions of de-regulated cytokines are summarized in Table 2.

Considering NfL and GFAP levels, as expected, significant increases were observed between SMC and both NC and PMC: NfL mean levels (pg/ml) ± SEM were 59.05 ± 5,91 versus 9.75 ± 0,78 in NC and14,10 ± 2.20 in PMC, $P<0.0001$ and GFAP levels were 186.30 ± 10.26 versus 106.2 ± 12.17 in NC and 102,2 ± 06.10 in PMC, $P<0,0001$. These differences in mean values remained significant even when stratifying

Table 2
De-regulated cytokine and chemokine main functions.

Cytokine/ Chemokine	Main functions
TNF-α	• Secreted by macrophages. • Functions through its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR • Involved in the regulation of cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation
IL-1α	• Pleiotropic cytokine involved in various immune responses, inflammatory processes and hematopoiesis
IL-1β	• Important mediator of the inflammatory response • Involved in cell proliferation, differentiation and apoptosis
IL-6	• Produced at sites of acute and chronic inflammation, where it is secreted into the serum and induces a transcriptional inflammatory response through interleukin 6 receptor, alpha
IL-7	• Important for B and T cell development • Plays an essential role in lymphoid cell survival and in the maintenance of naive and memory T cell
IL-10	• Produced primarily by monocytes • Has pleiotropic effects in immunoregulation and inflammation • Down-regulates the expression of Th1 cytokines, MHC class II antigens, and costimulatory molecules on macrophages • Enhances B cell survival, proliferation, and antibody production
IL-12/IL-23p40	• Activate the transcription activator STAT4 • Stimulate the production of interferon-gamma
IL-15	• Regulates T and natural killer cell activation and proliferation
IL-16	• Pleiotropic cytokine that functions as a chemoattractant, a modulator of T cell activation and an inhibitor of HIV replication
IL-17A	• Induce the production of inflammatory molecules, chemokines, antimicrobial peptides and remodeling proteins • Elicits crucial impacts on host defense, cell trafficking, immune modulation, and tissue repair, with a key role in the induction of innate immune defences • Stimulates non-hematopoietic cells and promotes chemokine production by attracting myeloid cells to inflammatory sites
Eotaxin	• Antimicrobial • Involved in immunoregulatory and inflammatory processes • Displays chemotactic activity for eosinophils, but not mononuclear cells or neutrophils.
Eotaxin-3	• Potent eosinophil chemoattractant • Elevated in peripheral blood during active inflammation
IP-10	• Antimicrobial • Pleiotropic effects, including stimulation of monocytes, natural killer and T-cell migration, and modulation of adhesion molecule expression
MCP-1	• Displays chemotactic activity for monocytes and basophils but not for neutrophils or eosinophils

symptomatic patients by the mutated gene ($P<0.0001$).

Considering instead the levels of NfL, GFAP, and the altered inflammatory molecules, no significant correlations emerged.

4. Discussion

Herein, we showed that inflammatory proteins are upregulated in *MAPT* and *GRN* SMC, with some specific factors altered in *GRN* only, whereas no changes were seen in C*9ORF72* carriers. Notably, the only down regulated cytokine was IL-1α, which was decreased not only in SMC but also in PMC, independent of the type of causal mutation.

The similarity of alterations seen between *GRN* and *MAPT* was unexpected, considering that they are associated with different pathogenic proteins. Moreover, whereas it is known that PGRN has anti-inflammatory properties and thus its haploinsufficiency may favour an inflammatory environment, the same does not apply to tau protein, although evidence of neuroinflammation is shared among almost all neurodegenerative diseases (Masrori et al., 2022). Several inflammatory factors were specifically increased in *GRN* SMC, some of which already

shown in literature, such as IL-6 (Bossù et al., 2011; Gibbons et al., 2015). As regards *GRN*, we cannot exclude specific effects of different mutations, but only those related to the haploinsufficiency mechanism were considered here, thus making this possibility unlikely.

According to our results, it seems that inflammation is not associated with symptomatic stages of *C9ORF72* carriers. In line with these results, Katisco et al. showed that out of 8 cytokines analysed in patients carrying the *C9ORF72* mutation as compared with sporadic patients, only IL-10 was increased in carriers, but specifically in males (Katisko et al., 2020).

The only exception to up-regulation is IL-1α: notably, significant results were found in *GRN* and *C9ORF72* SMC, and in *MAPT* SMC it was so decreased to be undetectable in many samples with the method used. This cytokine was also downregulated in all PMC, suggesting that it begins to decrease early in the preclinical phase and continues to diminish during the symptomatic phase.

Regarding IL-1β a previous study from the GENFI consortium showed that its levels are increased in SMC as compared with NC (Ullgren et al., 2023), although no stratification according to the mutated gene was considered. Here, we confirm these results, which seem to be driven mostly by *GRN* SMC.

Interestingly, IL1α and IL1β are part of the same cluster on chromosome 2. IL1α is a pleiotropic cytokine, produced by monocytes and macrophages as a proprotein, involved in various immune responses, inflammatory processes, and haematopoiesis. IL-1 α is produced by activated macrophages as a proprotein, which is proteolytically processed to its active form by caspase 1. It is an important mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. Both signal via the same receptor, and are translated into 31 kDa pro-forms. However, unlike pro-IL-1β, pro-IL-1α has a functional nuclear localization signal (NLS) in the N-terminal domain (Wessendorf et al., 1993; Luheshi et al., 2009). In epithelial cells, myeloid cells, and keratinocytes, pro-IL-1α is shuttled to the nucleus upon translation (Malik and Kanneganti, 2018). Therefore, low circulating levels of this cytokine could be related to its nuclear translocation, where it would be able to recruit adapter molecules such as MYD88, IRAK1 or IRAK4 (Brikos et al., 2007), which in turn mediate the activation of NF-kappa-B and the three MAPK pathways p38, p42/p44 and JNK pathways (Wu et al. 2004).

This study revealed that inflammatory proteins are upregulated in symptomatic carriers of *MAPT* and *GRN* mutations, with specific changes in *GRN* only, while no changes are seen in *C9ORF72* carriers. IL-1α is notably downregulated in both symptomatic and pre-symptomatic carriers. These findings suggest shared inflammatory pathways between *GRN* and *MAPT*, indicating potential common therapeutic targets. The results also highlight the potential of IL-1α as a longitudinal biomarker for disease progression. Clinically, recognizing distinct inflammatory profiles can guide the development of tailored therapies and improve diagnostic and prognostic tools. Early monitoring of inflammatory markers could prompt preventive interventions, slowing disease progression and improving outcomes. Overall, these findings underscore the critical role of inflammation in genetic FTD, paving the way for targeted therapies, improved diagnostics, and personalized care (Asken et al., 2023; Bossù et al., 2011; Gibbons et al., 2015; Katisko et al., 2020; Masrori et al., 2022; Ullgren et al., 2023).

Considering gender stratification, some intriguing gender-specific differences in inflammatory markers were observed. In male *GRN* and *MAPT* SMC, IL-15 levels were significantly increased, suggesting a gender-specific immune response. Female SMC, however, do not show significant differences in IL-15 levels. In contrast, IL-17A levels were significantly elevated only in female SMC, indicating a unique inflammatory response in women.

Focusing on *GRN* SMC, IL-6 levels were significantly higher in females, highlighting a possible gender-specific pathogenesis in FTD. Moreover, elevated IP-10 levels in males could indicate a more pronounced or different inflammatory pathway activation compared to females. This might contribute to differences in disease manifestation, progression, or response to treatment between genders. These findings align with Piscopo et al. (2021), who emphasized the impact of gender on FTD biomarkers, highlighting the need for gender-specific analyses in research and treatment. Globally, these gender-specific differences in IL-15, IL-17A, IL-6, and IP-10 levels underline the complexity of FTD and the necessity for personalized treatment approaches.

Despite all these evidence in the literature supporting a role of gender in the distribution of marker levels in neurodegenerative diseases (Katisko et al., 2020, Piscopo et al., 2021), it is essential to consider the imbalance in the number of male and female subjects in each group in this specific case FTD population. This imbalance could contribute to the observed significances and may affect the statistical power and reliability of the results, necessitating caution in interpreting these findings.

A strength of the study is represented by NC from the same families, reducing the genetic background, which could influence inflammatory factor levels. A weakness of the study is instead that we did not compare the same subjects from the asymptomatic to the symptomatic phase. A recent study showed in fact that concentration of plasma TNFα levels predict future clinical decline in patients with asymptomatic genetic FTD (Asken et al., 2023). As regards the longitudinal analysis of PMC, the follow up of participants in GENFI is ongoing and these findings could be confirmed longitudinally in the next future. So far, the best prediction of the time to overt symptoms in PMC is the mean age at onset of the family, which is however a rough measure and though a limitation of the study.

This study offers valuable insights into FTD by identifying shared inflammatory pathways between *GRN* and *MAPT* mutations, suggesting that inflammation-targeting therapies might be effective across multiple genetic forms of FTD. The consistent downregulation of IL-1α across disease stages highlights its potential as a biomarker for early detection and monitoring, facilitating earlier intervention and tracking of disease progression. Understanding distinct inflammatory profiles can guide the development of targeted therapies, improving diagnostic and prognostic tools.

Future research should validate these findings in larger cohorts, explore the mechanisms behind shared inflammatory pathways, and develop anti-inflammatory therapies tailored to specific genetic profiles. Longitudinal studies are needed to confirm the reliability of inflammatory markers like IL-1α and TNFα as biomarkers. Integrating these markers into clinical practice requires standardized protocols, clinician training, and incorporation into patient management guidelines. Overall, this study advances the understanding of inflammation in genetic FTD, paving the way for targeted therapies, improved diagnostics, and personalized patient care.

5. Conclusion

We showed that inflammatory proteins are upregulated in *MAPT* and *GRN* SMC, with some specific factors altered in *GRN* only, whereas no changes were seen in *C9ORF72* SMC. Notably, the only downregulated cytokine found was IL-1α which levels were decreased not only in SMC but also in PMC, independently of the type of causal mutation, suggesting common modification occurring in the preclinical phase of the disease.

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Chiara Fenoglio: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Maria Serpente:** Methodology, Investigation, Data curation. **Marina Arcaro:** Methodology. **Tiziana Carandini:** Resources. **Luca Sacchi:** Resources. **Manuela Pintus:** Resources. **Emanuela Rotondo:** Resources. **Vittoria Borracci:** Resources. **Laura Ghezzi:** Resources. **Arabella Bouzigues:** Resources. **Lucy L. Russell:** Resources. **Phoebe H. Foster:** Resources. **Eve Ferry-Bolder:** Resources. **John C. van Swieten:** Resources. **Lize C. Jiskoot:** Resources. **Harro Seelaar:** Resources. **Raquel Sánchez Valle:** Resources. **Robert Laforce:** Resources. **Caroline Graff:** Resources. **Rik Vandenberghe:** Resources. **Alexandre de Mendonça:** Resources. **Pietro Tiraboschi:** Resources. **Isabel Santana:** Resources. **Alexander Gerhard:** Resources. **Johannes Levin:** Resources. **Sandro Sorbi:** Resources. **Markus Otto:** Resources. **Florence Pasquier:** Resources. **Simon Ducharme:** Resources. **Chris R. Butler:** Resources. **Isabelle Le Ber:** Resources. **Elizabeth Finger:** Resources. **Maria Carmela Tartaglia:** Methodology, Investigation, Data curation. **Mario Masellis:** Resources. **James B. Rowe:** Resources. **Matthis Synofzik:** Resources. **Fermin Moreno:** Resources. **Barbara Borroni:** Resources. **Jonathan D. Rohrer:** Resources. **Andrea Arighi:** Writing – review & editing. **Daniela Galimberti:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Anonymized data may be shared upon request from a qualified academic investigator for the purpose of replication of procedures and results detailed in this article. All requests must be in agreement with EU legislation on general data protection and must be in line with the decisions from the Italian Ethical Review Board. Data sharing should be regulated in a material transfer agreement and/or data processing agreement as appropriate.

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Appendix A. Supplementary data

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