Differential lipid mediator involvement in the different forms of genetic frontotemporal dementia – novel insights into neuroinflammation

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Keywords: lipid mediators; frontotemporal dementia; neuroinflammation, progranulin, C9orf72, tau

Abstract

Background: The pathophysiology of frontotemporal dementia (FTD) is poorly understood but recent studies implicate neuroinflammation. However, little is known so far about the role of the resolution pathway, the response to inflammation that allows tissue to return to a homeostatic state.

Objective: We aimed to measure the concentrations of lipid mediators including specialized proresolving mediators (SPMs) and proinflammatory eicosanoids in the cerebrospinal fluid (CSF) of people with FTD.

Methods: 15 people with genetic FTD (5 with *C9orf72* expansions, 5 with *GRN* mutations, and 5 with *MAPT* mutations) were recruited to the study along with 15 age- and sex-matched healthy controls. Targeted liquid chromatography-tandem mass spectrometry techniques were used to measure the CSF concentrations of lipid mediators in the docosahexaenoic acid (DHA), n-3 docosapentaenoic acid, eicosapentaenoic acid and arachidonic acid (AA) metabolomes. Concentrations were compared using linear regression models, with bootstrapping for data that was not normally distributed.

Results: C9orf72 expansion carriers had higher concentrations of SPMs: DHA-derived maresins (controls mean 0.6 (standard deviation 1.6) pg/mL, *MAPT* 4.6 (7.9), *C9orf72* 7.1 (5.9), *GRN* 0.0 (0.0)) and DHA-derived resolvins (controls 1.3 (2.9) pg/mL, *MAPT* 0.9 (0.7), *C9orf72* 7.7 (4.7), *GRN* 0.6 (1.0)). In contrast, *GRN* and MAPT mutation carriers had normal concentrations of SPMs but significantly higher concentrations of the proinflammatory AA-derived leukotrienes (controls 0.0 (0.1) pg/mL, *MAPT* 0.4 (0.5), *C9orf72* 0.3 (0.3), *GRN* 0.4 (0.2)), and AA-derived thromboxane (controls 0.8 (1.0) pg/mL, *MAPT* 3.1 (1.8), *C9orf72* 2.4 (2.2), *GRN* 1.8 (0.7)). Additionally, the *C9orf72* expansion carriers also had significantly higher concentrations of AA-derived leukotrienes.

Conclusion: This initial pilot study of lipid mediators provides a window into a novel biological pathway not previously investigated in FTD, showing differential patterns of alterations between those with *C9orf72* expansions (where SPMs are higher) and *GRN* and *MAPT* mutations (where only proinflammatory eicosanoids are higher).

Introduction

The term frontotemporal dementia (FTD) encompasses a group of neurodegenerative disorders with a wide spectrum of clinical manifestations and complex disease mechanisms[1]. FTD is a highly heritable disorder, with the majority of genetic FTD caused by mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*)[2–4]. In common with other neurodegenerative diseases, inflammation appears to play a crucial role in the development of FTD and both molecular and clinical studies over recent years have highlighted its importance (reviewed in Bright et al [5]). Neuroinflammation is complex and involves multiple stages: once it is triggered there is activation of glial cells with upregulation of several proteins, including cytokines and chemokines, that help guide the process. However, consistent inflammatory activation destroys the healthy structures surrounding the inflammatory core and leads to cellular necrosis or apoptosis. A regulatory mechanism that ameliorates inflammation-related damage is therefore required, and this is the process called 'resolution', which emerges after innate and adaptative inflammation has occurred[6]. Resolution involves a number of cellular processes that promote removal of dead cells and debris, restoration of vascular integrity and perfusion, and regeneration of tissue[7]. Key to the process of resolution are the specialized proresolving lipid mediators (SPMs) that are synthesized by a variety of cells including endothelial cells, macrophages and neutrophils [8]. Whilst studies have started to investigate the presence of measures of microglial activation, cytokines, chemokines and complement proteins in the biofluids of people with FTD (reviewed in Swift et al [9]), there has been little investigation of SPMs and how the resolution pathway might be altered in FTD [10]. However, recent studies have suggested that impaired resolution may be a contributing mechanism leading to chronic inflammation in dementia[11].

Although the majority of lipid mediators are involved in resolution (Figure 1), a number of those derived from arachidonic acid (eicosanoids) are in fact proinflammatory [12-14] and whilst little is

currently known about their role in FTD, they have previously been shown to exacerbate pathology in Alzheimer's disease [13,14].

We therefore set out to measure the lipid mediators underlying the resolution pathway (SPMs), as well as the closely related proinflammatory eicosanoids, in the cerebrospinal fluid (CSF) of a group of people with genetic FTD.

Methods

Participants

Fifteen people with genetically-confirmed symptomatic FTD (5 with *MAPT* mutations, 5 with *GRN* mutations, and 5 with *C9orf72* expansions) with available CSF were consecutively recruited from the University College London Genetic FTD Initiative study. The group consisted of 10 men and 5 women, with a mean (standard deviation) age of 63.8 (5.7) years old at sample collection. In the individual genetic groups: *MAPT* 3 men, 2 women, 63.1 (4.2) years old; *C9orf72* 4 men, 1 woman, 63.4 (6.9) years old; *GRN* 3 men, 2 women, 64.8 (6.7) years old. 15 healthy controls were recruited over the same time period: 10 men and 5 women, 64.0 (5.9) years old. No significant differences were seen between groups in terms of age or sex.

Targeted lipid mediator profiling

All samples were extracted using solid-phase extraction columns as previously described [15]. Prior to sample extraction, deuterated internal standards, representing each region in the chromatographic analysis were added to facilitate quantification in 4 vol of cold methanol. Lipid mediators were then measured via liquid chromatography tandem mass spectrometry using targeted multiple reaction monitoring. Each lipid mediator was identified using established criteria, including matching retention time to synthetic and authentic materials and at least 6 diagnostic ions. Calibration curves were

obtained for each using synthetic compound mixtures at 0.78, 1.56, 3.12, 6.25, 12.5, 25, 50, 100, and 200 pg, which gave linear calibration curves with r^2 values of 0.98–0.99 [15].

Lipid mediators in the following groups were identified: 1) in the docosahexaenoic acid (DHA) metabolome, maresins, protectins and resolvins; 2) in the n-3 docosapentaenoic acid (n-3 DPA) metabolome, maresins, protectins and resolvins (D-series and 13-series); 3) in the eicosapentaenoic acid (EPA) metabolome, resolvins; and 4) in the arachidonic acid (AA) metabolome, lipoxins, leukotrienes, prostaglandins, and thromboxane. Concentrations of individual lipid mediators were combined to give a single measure for each of the 12 groups outlined above. This is detailed in Supplementary Table 1 (and previously described in [15]). Of note, the leukotrienes, prostaglandins and thromboxanes are proinflammatory eicosanoids whilst the other measures are all SPMs.

Statistical analysis

All statistical analyses were performed in STATA (v.16). The concentrations of each measure were compared between groups using non-parametric tests: the Wilcoxon Rank Sum test for comparison between the total FTD group and controls and the Kruskal-Wallis test (with post hoc pairwise tests) for comparisons between the individual genetic groups and controls. Spearman correlation coefficients were determined to investigate the relationship between the concentrations of each measure and disease duration.

Results

Concentrations were below the lower limit of detection for the n-3 DPA-derived protectins and n-3 DPA-derived D-series resolvins. However, differences were seen between groups in four of the other ten measures (Table 1, Figure 2). Amongst the SPMs, concentrations were higher in the *C9orf72* expansion carriers for the DHA-derived maresins (controls mean 0.6 (standard deviation 1.6) pg/mL, *MAPT* 4.6 (7.9), *C9orf72* 7.1 (5.9), *GRN* 0.0 (0.0)) and the DHA-derived resolvins (controls 1.3 (2.9)

pg/mL, *MAPT* 0.9 (0.7), *C9orf72* 7.7 (4.7), *GRN* 0.6 (1.0)) in comparison with controls and the *GRN* mutation carriers (but not with the *MAPT* group). No differences were seen in the *MAPT* or *GRN* mutation carriers compared with controls, although concentrations of the DHA-derived maresins were positively correlated with disease duration in the *MAPT* group (rho = 0.89, p=0.041). No other significant correlations were seen comparing SPMs with disease duration apart from in *C9orf72* expansion carriers for n-3 DPA-derived 13-series resolvins levels (rho = -0.89, p=0.041).

In contrast, both the *GRN* and *MAPT* mutation carriers had significantly higher concentrations of the AA-derived leukotrienes (controls 0.0 (0.1) pg/mL, *MAPT* 0.4 (0.5), *C9orf72* 0.3 (0.3), *GRN* 0.4 (0.2)), and AA-derived thromboxane (controls 0.8 (1.0) pg/mL, *MAPT* 3.1 (1.8), *C9orf72* 2.4 (2.2), *GRN* 1.8 (0.7)) compared with controls. The AA-derived leukotrienes were also higher than controls in the C9orf72 group. For the AA-derived leukotrienes, concentrations were strongly positively correlated with disease duration in the *MAPT* group: rho = 0.97, p=0.005. No other correlations were found in any of the groups comparing proinflammatory eicosanoid levels with disease duration.

Discussion

In this preliminary study, we show that SPMs and the proinflammatory eicosanoids are abnormal in genetic FTD, with a differential pattern in the different forms: the SPMs are higher in concentration in *C9orf72* mutation carriers but normal in *GRN* and *MAPT* mutation carriers whilst the proinflammatory eicosanoids are higher in *GRN* and *MAPT* mutation carriers with only AA-derived leukotrienes higher in *C9orf72* mutation carriers.

Only one previous study has investigated SPMs in FTD: Fraga and colleagues studied the levels of the lipoxin LXA_4 and found no differences in behavioural variant FTD in either plasma or CSF compared to healthy controls or people with Alzheimer's disease (AD)[10]. In contrast, studies of AD have shown abnormalities of SPMs both in tissue and CSF e.g. downregulation of DHA-derived mediators such as

MaR1, PD1, and RvD5 as well as LXA_4 is seen in the entorhinal cortex and hippocampus[16,17], whilst concentrations of LXA_4 are lower in the CSF of people with AD[18], suggesting that the impairment of resolution may potentiate chronic inflammation in AD[11]. Intriguingly, we found the opposite pattern in *C9orf72*-related neurodegeneration with increased levels of SPMs. One prior study of DHA-derived resolvins does in fact show increased levels in the spinal cord tissue of people with ALS [19], one of the phenotypes of *C9orf72* expansions. The mechanisms of how this affects the pathophysiology of FTD or ALS remains unclear, and further studies both in tissue and biofluids will be important to understand this more clearly.

The finding of abnormal proinflammatory eicosanoids in *GRN* mutation carriers is consistent with previous studies showing that inflammation plays a major role in this form of FTD [5, 20]. In CSF, abnormalities have previously been shown in microglial activation markers [21–24], chemokines and cytokines [20,25], and complement proteins [26]. Here, we add to these findings, suggesting a further biomarker that may be useful in disease modifying trials – lowering of the concentrations of the proinflammatory eicosanoids may help to show a therapeutic effect in *GRN*-related FTD with improvement of chronic neuroinflammation, although more validation work would need to be done in the first instance. An increase in proinflammatory eicosanoids was seen in *MAPT*-related FTD as well – this group has also been previously associated with abnormal neuroinflammation in prior studies [27]. Only an increase in the AA-derived leukotrienes was seen in the *C9orf72* group, likely due to the complex nature of neuroinflammation and the different pathways affected.

Although there has been little work in SPMs in FTD, there is a growing literature on the involvement of lipids in the pathophysiology of the disease [28–30], including biomarker studies in CSF. One study showed an association with survival [30] (with cholesterol levels), whilst a lipidomic study found widespread abnormalities in different lipid species [29]. However, most of the studies so far have

focused on clinically-defined populations with the association of abnormal lipid processing in FTD and underlying molecular pathology remaining unclear.

The limitations of the study include the small number of cases investigated here, reducing the power to detect changes. However, even with these small numbers, we found differences within the genetic groups. Further studies will be needed to extend this pilot investigation, including a wider group of mutation carriers across the spectrum from the presymptomatic to symptomatic stages. Another limitation was the lack of data collected on concurrent medication including particularly anti-inflammatory drugs – such information will be an important factor to take into account in future studies.

Overall, our results suggest that there are differential alterations in SPMs and proinflammatory eicosanoids in the different forms of genetic FTD and that these changes can be detected and monitored in CSF supporting the use of such lipids as biomarkers to understand underlying disease pathophysiology in FTD, and potentially as markers of neuroinflammation in future therapeutic trials. Further studies will be needed in a larger cohort, including in very early disease, to determine when and how alterations of lipid mediators occur, and how they change over time.

Declarations

Ethics approval

The London Queen Square Ethics committee approved the study.

Consent for publication

All participants provided written informed consent at enrolment including consent to publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

JDR has served on medical advisory boards and consultancy for Alector, Arkuda Therapeutics, Wave Life Sciences, and Prevail Therapeutics. Consultancy for UCB, AC Immune, Astex Pharmaceuticals, Biogen, Takeda and Eisai.

Funding

The Dementia Research Centre is supported by Alzheimer's Research UK, Alzheimer's Society, Brain Research UK, and The Wolfson Foundation. This work was supported by the NIHR UCL/H Biomedical Research Centre, the Leonard Wolfson Experimental Neurology Centre (LWENC) Clinical Research Facility, and the UK Dementia Research Institute, which receives its funding from UK DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. ASE is supported by the UK Dementia Research Institute which receives its funding from DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. JDR has received funding from an MRC Clinician Scientist Fellowship (MR/M008525/1) and the NIHR Rare Disease

Translational Research Collaboration (BRC149/NS/MH) as well as the Brain Research UK Miriam Marks Fellowship; his work is also supported by the MRC UK GENFI grant (MR/M023664/1), the Bluefield Project and the JPND GENFI-PROX grant (2019-02248). This work was also supported by funding from the Barts Charity (grant no: MGU0343) to JD.

Authors' contributions

RAC and JD analysed the samples. ASE and JDR analysed and interpreted the data and wrote the initial draft of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank the research participants for their contribution to the study.

References

[1] Rohrer JD, Zetterberg H (2014) Biomarkers in frontotemporal dementia. *Biomark Med* **8**, 519–521.

[2] Greaves C V., Rohrer JD (2019) An update on genetic frontotemporal dementia. *J Neurol* **266**, 2075–2086.

[3] Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, van Minkelen R, Rombouts SA, Cardoso MJ, Clegg S, Espak M, Mead S, Thomas DL, De Vita E, Masellis M, Black SE, Freedman M, Keren R, MacIntosh BJ, Rogaeva E, Tang-Wai D, Tartaglia MC, Laforce R, Tagliavini F, Tiraboschi P, Redaelli V, Prioni S, Grisoli M, Borroni B, Padovani A, Galimberti D, Scarpini E, Arighi A, Fumagalli G, Rowe JB, Coyle-Gilchrist I, Graff C, Fallström M, Jelic V, Ståhlbom AK, Andersson C, Thonberg H, Lilius L, Frisoni GB, Pievani M, Bocchetta M, Benussi L, Ghidoni R, Finger E, Sorbi S, Nacmias B, Lombardi G, Polito C, Warren JD, Ourselin S, Fox NC, Rossor MN (2015) Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: A cross-sectional analysis. *Lancet Neurol* **14**, 253–262.

[4] Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, MacKenzie IRA, Warren JD, De Silva R, Holton J, Revesz T, Hardy J, Mead S, Rossor MN (2009) The heritability and genetics of frontotemporal lobar degeneration. *Neurology* **73**, 1451–1456.

[5] Bright F, Werry EL, Dobson-Stone C, Piguet O, Ittner LM, Halliday GM, Hodges JR, Kiernan MC, Loy CT, Kassiou M, Kril JJ (2019) Neuroinflammation in frontotemporal dementia. *Nat Rev Neurol* **15**, 540–555.

[6] Kamel H, Iadecola C (2012) Brain-immune interactions and ischemic stroke: Clinical implications. *Arch Neurol* **69**, 576–581.

[7] Basil MC, Levy BD (2016) Specialized pro-resolving mediators: Endogenous regulators of infection and inflammation. *Nat Rev Immunol* **16**, 51–67.

[8] Serhan CN (2007) Resolution phase of inflammation: Novel endogenous anti-inflammatory and

proresolving lipid mediators and pathways. *Annu Rev Immunol* **25**, 101–137.

[9] Swift IJ, Sogorb-Esteve A, Heller C, Synofzik M, Otto M, Graff C, Galimberti D, Todd E, Heslegrave AJ, Van Der Ende EL, Van Swieten JC, Zetterberg H, Rohrer JD (2021) Fluid biomarkers in frontotemporal dementia: Past, present and future. *J Neurol Neurosurg Psychiatry* **92**, 204–215.

[10] Fraga VG, Magalhães CA, Loures C de MG, de Souza LC, Guimarães HC, Zauli DAG, Carvalho M das G, Ferreira CN, Caramelli P, de Sousa LP, Gomes KB (2019) Inflammatory and Pro-resolving Mediators in Frontotemporal Dementia and Alzheimer's Disease. *Neuroscience* **421**, 123–135.

[11] Fraga VG, Carvalho M das G, Caramelli P, de Sousa LP, Gomes KB (2017) Resolution of inflammation, n − 3 fatty acid supplementation and Alzheimer disease: A narrative review. *J Neuroimmunol* **310**, 111–119.

[12] Tiberi M, Chiurchiù V (2021). Specialized Pro-resolving Lipid Mediators and Glial Cells: Emerging Candidates for Brain Homeostasis and Repair. *Front Cell Neurosci.* **15,** 673549.

[13] Biringer RG. The Role of Eicosanoids in Alzheimer's Disease (2009) *Int J Environ Res Public Health.* **16(14):**2560.

[14] Herbst-Robinson K, Liu L, James M, Yao Y, Xie SX, Brunder KR (2016). Inflammatory Eicosanoids Increase Amyloid Precursor Protein Expression via Activation of Multiple Neuronal Receptors. *Sci Rep.* **5:** 18286.

[15] Gomez EA, Colas RA, Souza PR, Hands R, Lewis MJ, Bessant C, Pitzalis C, Dalli J (2020) Blood pro-resolving mediators are linked with synovial pathology and are predictive of DMARD responsiveness in rheumatoid arthritis. *Nat Commun.* **11(1)**:5420.

[16] Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K, Serhan CN, Bazan NG (2005) A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J Clin Invest* **115**, 2774–2783.

[17] Zhu M, Wang X, Hjorth E, Colas RA, Schroeder L, Granholm AC, Serhan CN, Schultzberg M

(2016) Pro-Resolving Lipid Mediators Improve Neuronal Survival and Increase Aβ42 Phagocytosis. *Mol Neurobiol* **53**, 2733–2749.

[18] Wang X, Zhu M, Hjorth E, Cortés-Toro V, Eyjolfsdottir H, Graff C, Nennesmo I, Palmblad J, Eriksdotter M, Sambamurti K, Fitzgerald JM, Serhan CN, Granholm AC, Schultzberg M (2015) Resolution of inflammation is altered in Alzheimer's disease. *Alzheimer's Dement* **11**, 40-50.e2.

[19] Cacabelos D, Ayala V, Granado-Serrano AB, Jové M, Torres P, Boada J, Cabré R, Ramírez-Núñez O, Gonzalo H, Soler-Cantero A, Serrano JCE, Bellmunt MJ, Romero MP, Motilva MJ, Nonaka T, Hasegawa M, Ferrer I, Pamplona R, Portero-Otín M (2016) Interplay between TDP-43 and docosahexaenoic acid-related processes in amyotrophic lateral sclerosis. *Neurobiol Dis* **88**, 148–160.

[20] Galimberti D, Bonsi R, Fenoglio C, Serpente M, Cioffi SMG, Fumagalli G, Arighi A, Ghezzi L, Arcaro M, Mercurio M, Rotondo E, Scarpini E (2015) Inflammatory molecules in Frontotemporal Dementia: Cerebrospinal fluid signature of progranulin mutation carriers. *Brain Behav Immun* **49**, 182–187.

[21] Heywood WE, Hallqvist J, Heslegrave AJ, Zetterberg H, Fenoglio C, Scarpini E, Rohrer JD, Galimberti D, Mills K (2018) CSF pro-orexin and amyloid-β38 expression in Alzheimer's disease and frontotemporal dementia. *Neurobiol Aging* **72**, 171–176.

[22] Woollacott IOC, Nicholas JM, Heslegrave A, Heller C, Foiani MS, Dick KM, Russell LL, Paterson RW, Keshavan A, Fox NC, Warren JD, Schott JM, Zetterberg H, Rohrer JD (2018) Cerebrospinal fluid soluble TREM2 levels in frontotemporal dementia differ by genetic and pathological subgroup. *Alzheimer's Res Ther* **10**, 1–14.

[23] Woollacott IOC, Nicholas JM, Heller C, Foiani MS, Moore KM, Russell LL, Paterson RW, Keshavan A, Schott JM, Warren JD, Heslegrave A, Zetterberg H, Rohrer JD (2020) Cerebrospinal Fluid YKL-40 and Chitotriosidase Levels in Frontotemporal Dementia Vary by Clinical, Genetic and Pathological Subtype. *Dement Geriatr Cogn Disord* 1–21.

[24] Abu-Rumeileh S, Steinacker P, Polischi B, Mammana A, Bartoletti-Stella A, Oeckl P, Baiardi S,

Zenesini C, Huss A, Cortelli P, Capellari S, Otto M, Parchi P (2019) CSF biomarkers of neuroinflammation in distinct forms and subtypes of neurodegenerative dementia. *Alzheimer's Res Ther* **12**, 1–15.

[25] Galimberti D, Schoonenboom N, Scheltens P, Fenoglio C, Venturelli E, Pijnenburg YAL, Bresolin N, Scarpini E (2006) Intrathecal chemokine levels in Alzheimer disease and frontotemporal lobar degeneration. *Neurology* **66**, 146–147.

[26] Lui H, Zhang J, Makinson SR, Cahill MK, Kelley KW, Huang HY, Shang Y, Oldham MC, Martens LH, Gao F, Coppola G, Sloan SA, Hsieh CL, Kim CC, Bigio EH, Weintraub S, Mesulam MM, Rademakers R, MacKenzie IR, Seeley WW, Karydas A, Miller BL, Borroni B, Ghidoni R, Farese R V., Paz JT, Barres BA, Huang EJ (2016) Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation. *Cell* **165**, 921–935.

[27] Lant SB, Robinson AC, Thompson JC, Rollinson S, Pickering-Brown S, Snowden JS, Davidson YS, Gerhard A, Mann DM (2014). Patterns of microglial cell activation in frontotemporal lobar degeneration. *Neuropathol Appl Neurobiol.* **40(6):**686-96.

[28] Phan K, He Y, Pickford R, Bhatia S, Katzeff JS, Hodges JR, Piguet O, Halliday GM, Kim WS (2020) Uncovering pathophysiological changes in frontotemporal dementia using serum lipids. *Sci Rep* **10**, 1–13.

[29] Kim WS, Jary E, Pickford R, He Y, Ahmed RM, Piguet O, Hodges JR, Halliday GM (2018) Lipidomics analysis of behavioral variant frontotemporal dementia: A scope for biomarker development. *Front Neurol* **9**, 1–11.

[30] Ahmed RM, Highton-Williamson E, Caga J, Thornton N, Ramsey E, Zoing M, Kim WS, Halliday GM, Piguet O, Hodges JR, Farooqi IS, Kiernan MC (2017) Lipid Metabolism and Survival Across the Frontotemporal Dementia-Amyotrophic Lateral Sclerosis Spectrum: Relationships to Eating Behavior and Cognition. *J Alzheimer's Dis* **61**, 773–783.

Figure 1. Schematic representation of the role of lipid mediators in modulating neuroinflammation (adapted from *Tiberi et al, 2021* [12]).

Figure 2. Concentrations of proresolving and proinflammatory lipid mediators. Results expressed in pg/mL in controls and genetic FTD groups (MAPT, C9orf72 and GRN). Significant differences between groups shown by bars. Docosahexaenoic acid (DHA) metabolome, maresins (MaR), protectins (PD) and resolvins (RvD); in the n-3 docosapentaenoic acid (n-3 DPA) metabolome, maresins ($MaR_{n\text{-}3\ DPA}$), protectins ($PD_{n\text{-}3\ DPA}$) and resolvins (D-series ($RvD_{n\text{-}3\ DPA}$) and 13-series (RvT)); in the eicosapentaenoic acid (EPA) metabolome, resolvins (RvE); and in the arachidonic acid (AA) metabolome, lipoxins (LX), leukotrienes (LT), cysteinyl leukotrienes, prostaglandins (PG), and thromboxane (Tx).

Table 1. Demographics and mean (standard deviation) concentrations (pg/mL) for the lipid mediators in controls, the total FTD group and each of individual genetic groups (*MAPT, C9orf72* and *GRN* mutations). Significant differences between disease groups and controls are shown in bold: *p<0.05, **p<0.01, ***p<0.001. The only significant differences between individual genetic groups was between the *C9orf72* and *GRN* groups for DHA-derived maresins and DHA-derived resolvins (both p<0.05). N/A = not assessed as all values were at the lower limit of detection.

	Controls	Total FTD	*MAPT*	*C9orf72*	*GRN*
N	**15**	**15**	**5**	**5**	**5**
Age at CSF sampling (years)	64.0 (5.9)	63.8 (5.7)	63.1 (4.2)	63.4 (6.9)	64.8 (6.7)
Sex (% male)	66.7	66.7	60.0	80.0	60.0
Disease duration (years)	N/A	7.5 (5.6)	6.7 (3.5)	10.8 (7.7)	5.0 (4.0)
DHA-derived maresins	0.6 (1.6)	3.9 (6.1)	4.6 (7.9)	**7.1 (5.9)****	0.0 (0.0)
DHA-derived protectins	N/A	N/A	N/A	N/A	N/A
DHA-derived resolvins	1.3 (2.9)	3.1 (4.3)	0.9 (0.7)	**7.7 (4.7)***	0.6 (1.0)
n-3 DPA-derived maresins	0.0 (0.1)	0.1 (0.2)	0.1 (0.3)	0.1 (0.2)	0.0 (0.0)
n-3 DPA-derived protectins	N/A	N/A	N/A	N/A	N/A
n-3 DPA-derived D-series resolvins	N/A	N/A	N/A	N/A	N/A
n-3 DPA-derived 13-series resolvins	0.1 (0.3)	0.4 (0.7)	0.6 (0.9)	0.6 (0.8)	0.1 (0.2)
EPA-derived resolvins	0.4 (1.4)	4.9 (15.4)	0.9 (1.3)	13.0 (26.6)	0.9 (1.2)
AA-derived lipoxins	0.1 (0.2)	0.2 (0.5)	0.2 (0.3)	0.4 (0.8)	0.1 (0.1)
AA-derived leukotrienes	0.0 (0.1)	**0.3 (0.3)*****	**0.4 (0.5)****	**0.3 (0.3)***	**0.4 (0.2)*****
AA-derived prostaglandins	27.3 (18.0)	19.6 (10.9)	23.2 (13.8)	19.8 (8.4)	15.9 (10.9)
AA-derived thromboxane	0.8 (1.0)	**2.4 (1.7)****	**3.1 (1.8)****	2.4 (2.2)	**1.8 (0.7)***

Supplementary Table 1. Lipid mediators identified in each group

Lipid mediator group	Identified lipid mediators
DHA-derived maresins	MaR1; MaR2; 22-OH-MaR1; 14-oxo-MaR1; 7S,14SdiHDHA; 4S,14S-diHDHA
DHA-derived protectins	PD1; PD2; 17R-PD1; 10S,17S-diHDHA; 22-OH-PD1
DHA-derived resolvins	RvD1; RvD2; RvD3; RvD4; RvD5; RvD6; 17R-RvD1; 17R-RvD3
n-3 DPA-derived maresins	$MaR1_{n\text{-}3\ DPA}$; $MaR2n_{\text{-}3\ DPA}$; 7S,14SdiHDPA
n-3 DPA-derived protectins	$PD1_{n\text{-}3\ DPA}$; $PD2_{n\text{-}3\ DPA}$; 10S,17S-diHDPA
n-3 DPA-derived D-series resolvins	$RvD1_{n\text{-}3\ DPA}$; $RvD2_{n\text{-}3\ DPA}$; $RvD5_{n\text{-}3\ DPA}$
n-3 DPA-derived 13-series resolvins	RvT1; RvT2; RvT3; RvT4
EPA-derived resolvins	RvE1; RvE2; RvE3
AA-derived lipoxins	LXA_4; LXB_4; 5S,15S-diHETE; 15-epi-LXA_4; 15-epi- LXB_4; 15-oxo-LXA_4; 13,14-dehydro-15-oxo-LXA_4
AA-derived leukotrienes	LTB_4; 5S,12S-diHETE; 12-epi-6-trans LTB_4; 20-OH-LTB_4; 20-COOH-LTB_4; LTC_4; LTD_4; LTE_4
AA-derived prostaglandins	PGD_2; PGE_2; PGF_{2a}
AA-derived thromboxane	TxB_2