Inflammatory molecules in Frontotemporal Dementia: cerebrospinal fluid signature of progranulin mutation carriers

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BACKGROUND

- Mutations in progranulin gene (*GRN*) are one of the major causes of autosomal Frontotemporal Lobar Degeneration (FTLD) (Baker et al., 2006; Cruts et al., 2011). These cause haploinsufficiency and TAR DNA binding protein (TDP)-43 pathology (Neumann et al., 2006) .
- In central nervous system progranulin exerts different functions, as well as neuronal growth factor and it plays a central role in neuroinflammation. Infact:
  - ✓ It displays anti-inflammatory properties, but could also undergo cleavage to produce granulins, which have pro-inflammatory properties (Tang et al., 2011).
  - ✓ it regulates inflammatory cytokines and chemokines production (Yin Banerjee et al., 2010).

AIM

Analysis of cerebrospinal fluid (CSF) and serum profile of 27 inflammatory factors, including cytokines and chemokines, in patients with FTLD carrying *GRN* mutations as compared with sporadic FTLD patients and healthy age-matched non inflammatory and non demented controls.

POPULATION

	HEALTHY CONTROLS	FTD *GRN* carriers	FTD Sporadic
# serum (CSF)	19 (7)	12 (10)	16 (7)
Gender (M:F)	12:7	5:7	13:3
Mean age, years ± SD	64,5±14,4	66,3±7,0	75,2±6,7
Mean age at onset, years ± SD	-	64,6±6,1	71,9±7,0
Mean disease duration, years ± SD	-	3,9±2,6	3,3±1,8
Mean MMSE, score ± SD	28,9±1,8	19,2±5,5	18,5±8,0

MATERIALS & METHODS

DNA isolation & Genotyping:
Genomic DNA was isolated from whole blood using Flaxigene Kit (Qiagen).

- The entire open reading frame, including exon 0 and exon-intron boundaries of exons 1-12, of *GRN* gene was sequenced (Carecchio et al., 2009).
- *MAPT* exons 1 and 9-13 were analyzed by direct siquencing (Villa et al., 2011)
- The C9ORF72 genotyping was carried out by Repeat-Primed PCR (Xi et al., 2012)

Analytes determination:

- Aβ42, tau and P-tau levels were determinated with human specific ELISA kits (Fujirebio)
- Concentrations of immune analytes in sera were determinate using an ultrasensitive human 27-plex assay (Bio-Plex Pro Human Cytokine Group 27-Plex Panel, Bio-Rad).

RESULTS

	SERUM			CSF		
	CONTROLS	FTLD		CONTROLS	FTLD	
Analyte		Sporadic	GRN+		Sporadic	GRN+
Eotaxin	141,33	204,81	183,55	ND	ND	ND
FGF-basic	80,84	80,64	174,22	19,09	8,03	9,77
G-CSF	132,07	118,61	206,72	35,60	16,95	9,47
GM-CSF	37,49	70,46	27,22	23,83	15,65	30,50
IFN-ϒ	219,68	247,36	215,53	36,84	20,59	20,82
IL-1β	3,14	3,61	3,18	ND	ND	ND
IL-1Rα	156,14	176,40	286,66	12,36	11,30	6,23
IL-2	59,58	58,45	79,90	9,47	6,19	3,35
IL-4	12,00	11,00	11,63	ND	ND	ND
IL-5	17,68	14,08	10,74	ND	ND	ND
IL-6	19,35	22,81	20,37	4,39	4,31	2,91
IL-7	14,25	11,76	16,03	5,16	2,57	2,56
IL-8	68,82	77,06	74,49	19,93	28,20	18,96
IL-9	32,37	24,69	53,10	7,11	3,57	2,61
IL-10	15,46	12,86	36,12	6,82	4,48	2,62
IL-12	57,17	66,84	95,65	ND	ND	ND
IL-13	20,33	18,74	24,30	22,67	22,51	7,43
IL-15	31,22	30,73	32,88	19,15	12,30	9,34***
IL-17	471,84	355,89	498,96	15,37	9,45	8,46
IP-10	1277,29	1370,53	1451,17	436,61	644,94	809,17*
MCP-1	96,56	121,71	119,26	159,74	334,27°	187,29
MIP-1α	8,99	7,28	10,86	ND	ND	ND
MIP-1β	118,49	97,21	127,99	7,94	8,18	9,70
PDGF-BB	3790,38	3448,78	3078,73	ND	ND	ND
RANTES	12555,91	18216,73	9959,11	87,57	2,58#	4,63#
TNF-α	59,69	79,68	67,86	35,68	10,54	3,18**
VEGF	138,18	148,46	195,82	8,46	6,33	9,18

°p≤0,05 vs CTRLS
*p=0,012 vs CTRLS
**p=0,013 vs CTRLS
***p=0,023 vs CTRLS
#p<0.05 vs CTRLS

Table 1. Mean values of inflammatory molecules in CSF and serum

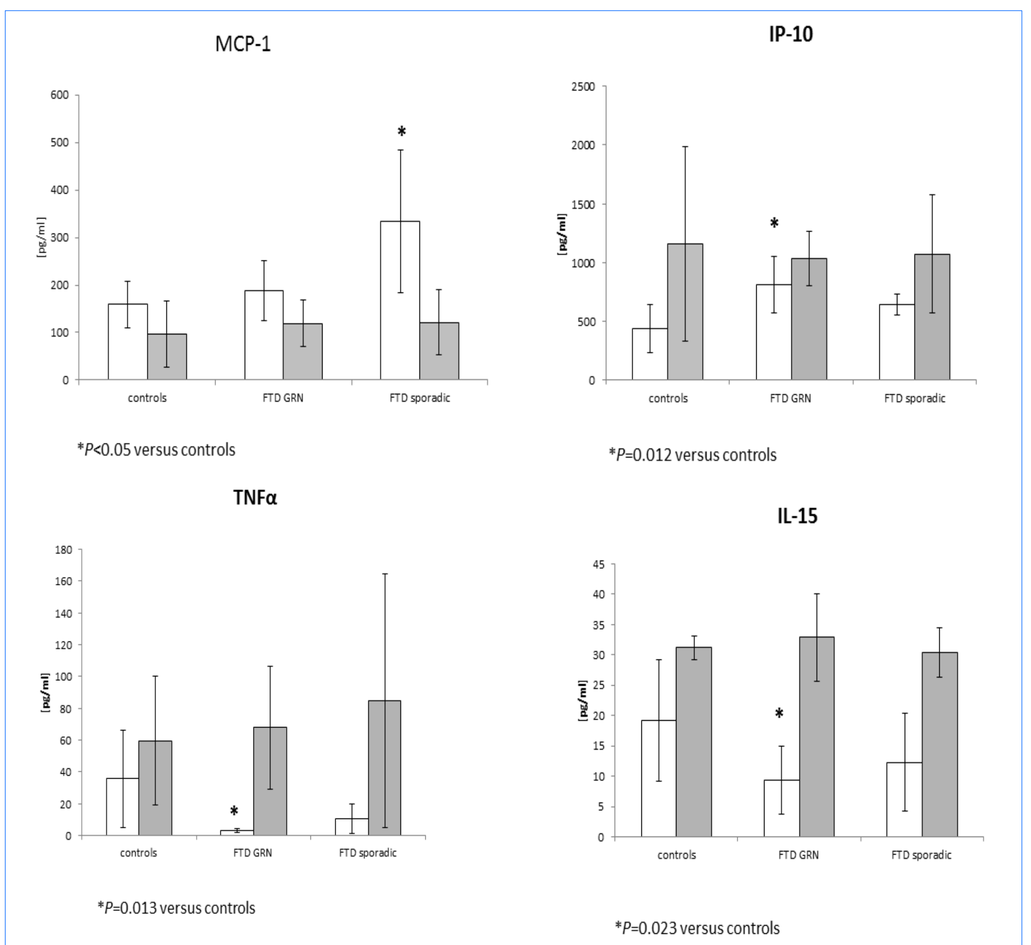


Figure 1. Mean CSF (white) and serum (grey)

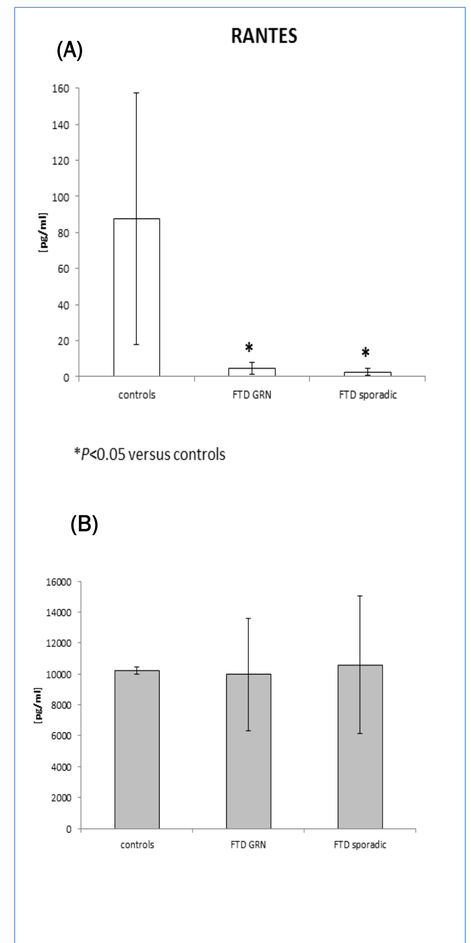
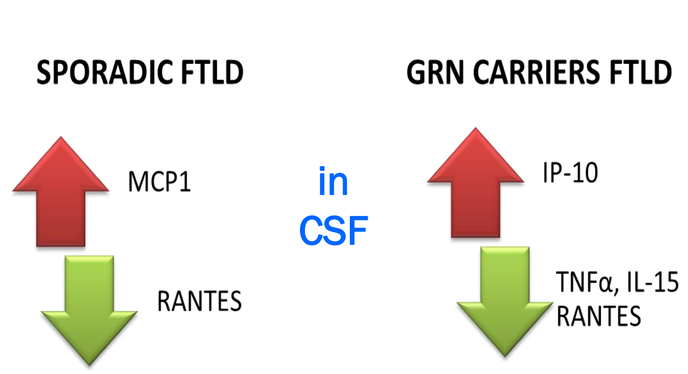


Figure 2. Mean RANTES levels in CSF (A) and serum (B)



- In serum no statistically differences between FTLD patients and controls were observed .
- Low TNFα or unchanged MCP-1 CSF levels in *GRN* carriers may be linked to haploinsufficiency
- Decreased CSF RANTES could result in the lack of neuroprotection

CONCLUSION

- In CSF of *GRN* mutation carriers there are increased levels of IP-10 and decreased levels of TNFα, IL15 and RANTES
- In CSF of sporadic FTLD patients there are increased levels of MCP-1 and decreased levels of RANTES
- These preliminary data possibly representing the basis for further studies to:
  - ✓ Better defining pathogenic pathway leading to neuronal death
  - ✓ Identify a biomarker for predicting the TDP-43 pathology
  - ✓ Identify novel targets for a tailored treatment

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