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Brief communication

Plasma levels of progranulin and interleukin-6 in frontotemporal lobar degeneration

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ABSTRACT

We have measured plasma progranulin and interleukin-6 in 230 patients with frontotemporal lobar degeneration (FTLD), 104 patients with Alzheimer's disease, and 161 control subjects. We have replicated previous findings of decreased levels of progranulin protein in FTLD because of mutations in *GRN* and show this is not observed in FTLD cases because of other causes. interleukin-6 levels were increased in FTLD overall, but these did not discriminate between clinical and genetic subtypes.

Frontotemporal lobar degeneration (FTLD) is the second most common cause of dementia in people younger than 65 years. The prototypical clinical syndromes are behavioral variant frontotemporal dementia, progressive nonfluent aphasia (PNFA), and semantic dementia (SD). Pathologically, about half of the cases show an accumulation of hyperphosphorylated tau proteins, some being associated with mutations in *MAPT*. Most others show an accumulation of the transactive DNA-binding protein, TDP-43, inherited cases being associated with mutations in progranulin (*GRN*) or hexanucleotide expansions in *C9ORF72*. However, when no gene mutation is known, it is not possible to accurately predict the underlying histology. A valid biological marker would not only help in formulating diagnosis, but could also serve as a potential index of treatment efficacy. Some progress has been made in this regard. Reductions in plasma levels of progranulin (PGRN) have been associated with *GRN* mutations (Finch et al., 2009; Ghidoni et al., 2008; Hsiung et al., 2011; Sleegers et al., 2009), and patients with FTLD have been reported to show increased cerebrospinal fluid or plasma levels of proinflammatory mediators (Sjorgen et al., 2004; Galimberti et al., 2006; Bossu et al., 2011).

We therefore measured plasma PGRN and interleukin-6 (IL-6) in patients with FTLD, Alzheimer's disease (AD), and healthy (spouse) control subjects to ascertain whether levels of these have potential to discriminate patients with FTLD from other neurodegenerative disorders (AD) and healthy individuals, and also whether they can differentiate between clinical, neurohistologic, and genetic subtypes of FTLD. We investigated 230 patients with FTLD, 104 patients with AD, and 161 healthy control subjects (Table 1). Patients with FTLD fulfilled current clinical diagnostic criteria (Harris et al., 2013), and clinical diagnosis of AD was consistent with International Consensus Clinical Criteria (McKhann et al., 1984). Of patients with FTLD, 117 had behavioral variant frontotemporal dementia, 31 had FTD + MND, 35 had SD, 42 had PNFA, and 5 had progressive apraxia (PAX) (Table 1). Ten patients with FTLD bore mutations in *GRN*, one had a *MAPT* mutation, and 13 bore hexanucleotide repeat expansions in *C9ORF72*. The control subjects were spouses of the patients. They were neither related to each other nor to the patients (except through marriage). The 3 diagnostic groups did not differ as to mean age at onset or duration of illness when sampled. Within the FTLD group, age at onset was later in patients with FTD + MND and PNFA than those with FTD, and age when sampled was later in patients with PNFA than those with FTD. Duration of illness when sampled was longer in patients with SD than those with FTD + MND. There were no significant differences for age at onset, age when sampled, and duration of illness when sampled between patients with the *GRN* mutation, patients with the *C9ORF72* mutation and

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Table 1
Mean (±SD) age at onset, age when sampled, current duration of illness, PGRN and IL-6 levels for patients with FTLD, both overall and when stratified according to clinical or genetic status, AD, and control subjects

Diagnostic group	Age at onset (y)	Age when sampled (y)	Duration (y)	PGRN (ng/mL)	IL-6 (pg/mL)
bvFTD (n = 117)	58.6 ± 8.9	62.5 ± 8.8	4.0 ± 3.0	54.7 ± 15.7	4.4 ± 3.4****
bvFTD + MND (n = 31)	64.4 ± 8.2*	67.2 ± 8.3	2.7 ± 1.5	56.6 ± 15.7	4.7 ± 1.8
SD (n = 35)	60.5 ± 6.0	65.7 ± 6.8	5.0 ± 3.0**	55.5 ± 13.6	4.3 ± 1.1
PNFA (n = 42)	65.2 ± 7.0*	68.6 ± 7.1*	3.4 ± 2.1	49.6 ± 13.4	3.8 ± 1.9
PAX (n = 5)	66.2 ± 14.7	69.7 ± 14.2	3.5 ± 1.9	49.0 ± 13.5	4.8 ± 1.1
All FTLD (n = 230)	61.1 ± 8.7	64.9 ± 8.7	3.9 ± 2.7	52.1 ± 17.1	4.3 ± 2.6
MAPT+ (n = 1)	58	58.9	0.9	39.2	1.9
GRN+ (n = 10)	59.8 ± 4.0	62.1 ± 4.7	2.4 ± 1.0	11.1 ± 5.0***	3.9 ± 0.9
C9ORF72 + (n = 13)	59.0 ± 8.2	62.7 ± 10.0	4.6 ± 4.8	61.0 ± 18.0	4.0 ± 0.9
Nonmutation bearers (n = 206)	61.2 ± 8.9	65.2 ± 8.7	3.9 ± 2.6	53.5 ± 14.6	4.3 ± 2.8
AD (n = 104)	62.3 ± 8.3	66.2 ± 8.1	3.7 ± 1.8	51.9 ± 12.6	3.1 ± 2.5
Controls (n = 161)	NA	65.1 ± 9.4	NA	53.7 ± 13.7	3.5 ± 3.4

Key: bvFTD, behavioral variant frontotemporal dementia; FTLD, frontotemporal lobar degeneration; IL-6, interleukin-6; NA, not applicable; PGRN, progranulin; SD, semantic dementia.
* $p < 0.006$ compared with bvFTD.
** $p < 0.01$ compared with bvFTD + MND.
*** $p < 0.001$ compared with C9ORF72+ and nonmutation bearers.
**** $p < 0.018$ and 0.001 compared with AD and controls, respectively.

nonmutation bearers (see Table 1). Blood samples were obtained with informed consent and full ethical approval. Plasma was separated routinely and stored at −80 °C until required for assay. PGRN and IL-6 were assayed in triplicate by enzyme-linked immunosorbent assay using specific high sensitivity commercially available kits (DPGRNO kit, R&D Systems for PGRN, Quantikine H&S kit for IL-6) in accordance with the manufacturer's recommendations. The limits of detection were 0.17 ng/mL for PGRN and 0.20 pg/mL for IL-6. PGRN was measured on all subjects, whereas IL-6 measures were performed on all except 2 of the FTLD patients, all except 2 of the AD patients and all except 3 of the control subjects, where insufficient sample remained to complete both assays. DNA was extracted from white blood cells separated from whole blood by routine centrifugation. Screening for mutations in *MAPT*, *GRN*, and expansions in *C9ORF72* had already been performed on all subjects. Most of *GRN* rs5848 genotypes were obtained using Sequenom Mass array genotyping assays using 15 ng of DNA, as per the manufacturer's instructions. Additional genotypes for *GRN* rs5848 and *TMEM106B* rs1020004, rs6966915, and rs1990622 SNPs was obtained using Applied Biosystems assay numbers C__7452046_20, and C__7604953_10, C_31573289_10 and C__11171598_10, respectively. A total of 10 ng of each DNA was amplified and genotyped on the 7700 Real time PCR system. Genotype calls were made using SDS v2.3 software (Applied Biosystems, Foster City, CA). All statistical

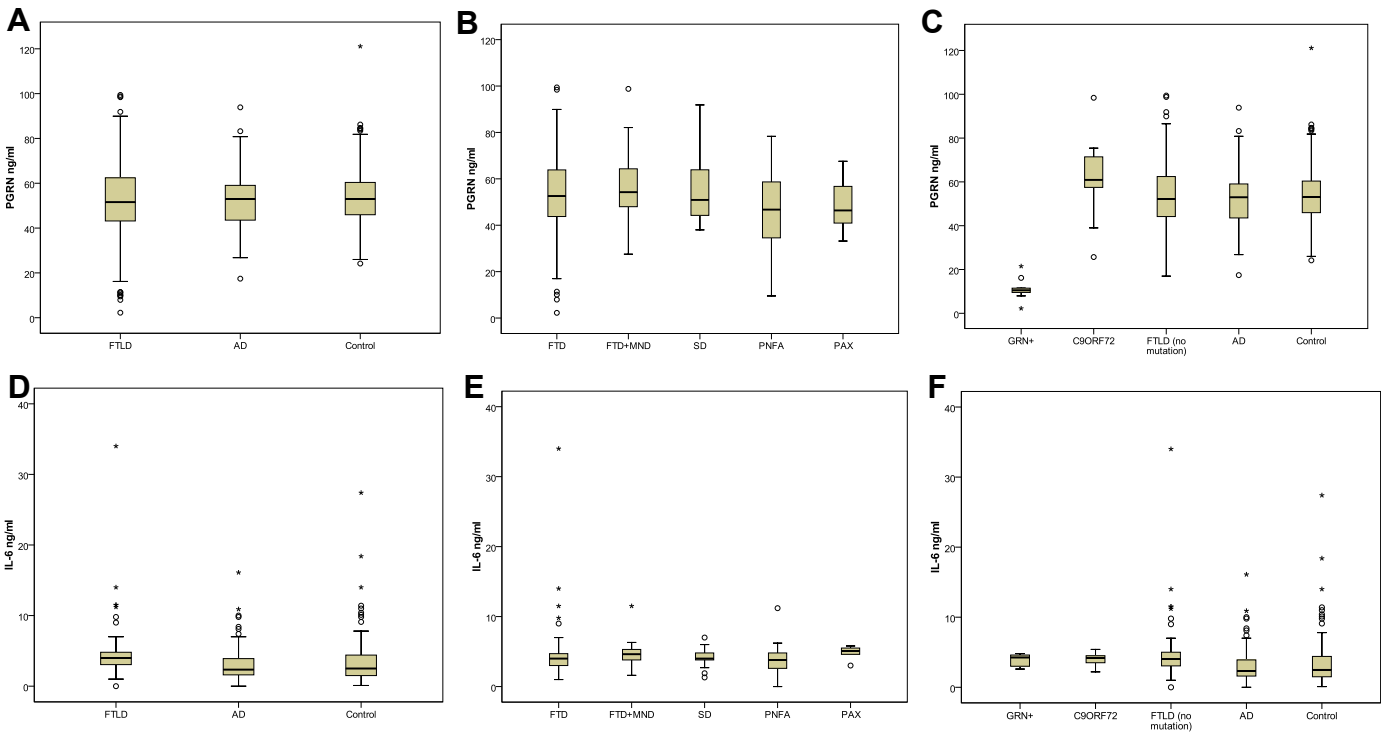

Fig. 1. Boxplots for measures of plasma PGRN (A-C) and IL-6 (D-F) levels for Frontotemporal Lobar degeneration (FTLD), Alzheimer's Disease (AD) and control groups, collectively, (A,C), and for FTLD groups stratified by clinical presentation into those with Frontotemporal dementia (FTD), FTD with Motor Neurone Disease (FTD+MND), Semantic dementia (SD), Progressive non-fluent Aphasia (PNFA) and Progressive Apraxia (PAX) (B,E), and by genetics into cases with GRN mutations, expansions in C9ORF72 or no known mutation (C,F).