INTRODUCTION. The frontotemporal lobar degeneration (FTLD) spectrum is clinically characterized by behavioural symptoms, language impairment, and deficits of executive functions [1,2]. Over the last few years, a number of causative gene mutations have been identified in FTLD patients, and the GRN Thr272fs mutations have been identified as a major cause of FTLD [3]. Nonetheless, the molecular mechanisms that link together gene mutations, neurodegeneration and clinical features of FTLD still remain largely unclear. We have recently shown that, despite similar disease duration, FTLD patients carriers of GRN Thr272fs mutation exhibit a more severe pattern of brain abnormalities than those with sporadic FTLD [4]. One of the missing elements in this complex picture is the potential role played by the white matter microstructure, which is already known to be altered in FTLD [5,6], and might represents the neuroanatomical substrate that links together GM loss and functional changes in broader networks. Aim of the current study was therefore to extend our previous investigation of FTLD patients carriers and non carriers of GRN Thr272fs mutation) [4], and to assess using diffusion MRI the contribution of microstructural WM damage in accounting for the more severe clinical features observed as driven by GRN Thr272fs mutation.

METHODS. This study included the following participants: 6 FTLD patients carriers of GRN Thr272fs mutation [GRN+] (F/M=3/3, mean (SD) age= 62.2 (4.3) years); 17 FTLD patients non mutation carriers [GRN-] (F/M=5/12, mean (SD) age= 67.6 (6.9) years); 12 healthy elderly subjects [HS] (F/M=8/4, mean (SD) age=60.7 (9.5) years). All subjects underwent a genetic assessment, a neuropsychological evaluation and an MRI scanning at 1.5 T including: 1) Dual echo turbo spin echo (TSE); 2) 3D magnetization–prepared rapid gradient echo (MPRAGE) T1-weighted scan; 3) Diffusion weighted Spin-Echo Planar imaging (SE-EPI).

The VBM analysis revealed a widespread pattern of atrophy in both groups of patients with respect to elderly healthy subjects. In particular patients carriers of GRN Thr272fs mutation showed a left medial frontal area of GM atrophy compared to patients non mutation carrier (Figure 1). The voxel-wise group comparisons of FA and MD in the CC1 showed widespread areas of reduced FA and increased MD in CC1 of patients with respect to elderly healthy subjects. But, more interestingly, GRN+ patients compared to GRN- patients showed anterior regions of FA reduction and increased MD in CC1 (Figure 1). Post-hoc Analysis: Given the anatomical proximity between the medial frontal cluster of reduced GM volume and CC1 (see Fig 1), we performed a post-hoc analysis investigating the association between the mean GM density (m-GM) of this cluster and FA and MD of CC1, voxel-wise.

DISCUSSION. Our study confirms previous results [4] of more severe GM volume loss in patients with FTLD and the GRN Thr272fs mutation. Moreover, it indicates that GRN+ patients have also more severe WM damage in the anterior part of the CC with respect to GRN- patients, as demonstrated by the voxel-wise analysis of FA and MD. Finally, we have also shown a correlation between GM atrophy of the medial frontal lobe and FA and MD of the adjacent WM. Although the correlation between WM and GM indices does not imply causality between the two events, it cannot be ruled out. We are in process of investigating the presence of correlations between these changes and clinical and neuropsychological scores.