White matter lesions in FTLD: distinct phenotypes characterize GRN and C9ORF72 mutations

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WHITE MATTER LESIONS IN FTLD: DISTINCT PHENOTYPES CHARACTERIZE *GRN* AND *C9ORF72* MUTATIONS

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Frontotemporal lobar degeneration (FTLD) has a high frequency of genetic forms; the 2 most common are *GRN* (progranulin) and *C9ORF72* mutations. Recently, our group reported extensive white matter (WM) lesions in 4 patients with FTLD caused by *GRN* mutation, in the absence of noteworthy cardiovascular risk factors,[1] in line with other studies in *GRN* mutation carriers.[2,3] Here we compared the characteristics of frontal WM lesions in patients with behavioral variant of FTLD (bv-FTLD) caused by *GRN* and *C9ORF72* mutations.

Methods. ***Patients.*** We retrospectively collected clinical and MRI data from 28 patients with a diagnosis of bv-FTLD based on the Rascovsky criteria,[4] including 11 *GRN* mutation carriers and 17 *C9ORF72* mutation carriers. One patient with multiple cardiovascular risk factors was excluded from this study; all other patients had no cardiovascular risk factors apart from sex, age, or treated and well-controlled hypertension. Age at onset was determined as the time of symptom appearance reported by the closest relative of the patient. A group of 11 age-matched healthy individuals were used as controls. Two *GRN* patients have been reported in a previous publication.[1] This retrospective study was approved by our institutional review board. Informed consent was obtained according to the French legislation for clinical genetic studies.

MRI. All patients had a brain MRI including fluid-attenuated inversion recovery (FLAIR) sequence (1.5T/3T, echo time >100 ms, slice thickness ≤5 mm). One neuroradiologist (F.A.) assessed the severity of left and right frontal atrophy using the Kipps-Davis scale for frontal atrophy.[5] Three neuroradiologists (F.A., S.S., and A. Bertrand) and 1 neurologist (P.C.) characterized the severity of WM lesions on FLAIR images in the left and right frontal lobes using an ad hoc 3-level visual score (figure). All readers were blinded to clinical and genetic data.

Statistical analysis was performed using GraphPad Prism 5.0 (San Diego, CA). Interrater agreements were assessed using the weighted κ test. Comparisons of sex and symptoms between the 3 groups were assessed using the χ^2 test; other comparisons were assessed using the Kruskal-Wallis test and Dunn post hoc test (when comparing 3 groups) or the Mann-Whitney test (when comparing 2 groups).

Results. No significant difference was observed between groups regarding sex, age at onset, age at MRI, disease duration, and associated amyotrophic lateral sclerosis symptoms (table e-1 at Neurology.org/ng).

Interrater agreement between the 4 readers for the characterization of WM lesions was moderate to very strong ($\kappa = 0.536$–0.805, median 0.74).

Frontal WM lesions were different between the 3 groups ($p = 0.007$ for the right side and $p < 0.0001$ for the left side, Kruskal-Wallis test). The grade of WM lesions was higher on both sides in the *GRN* group than in the control group and the *C9ORF72* group (Dunn post hoc test) (figure).

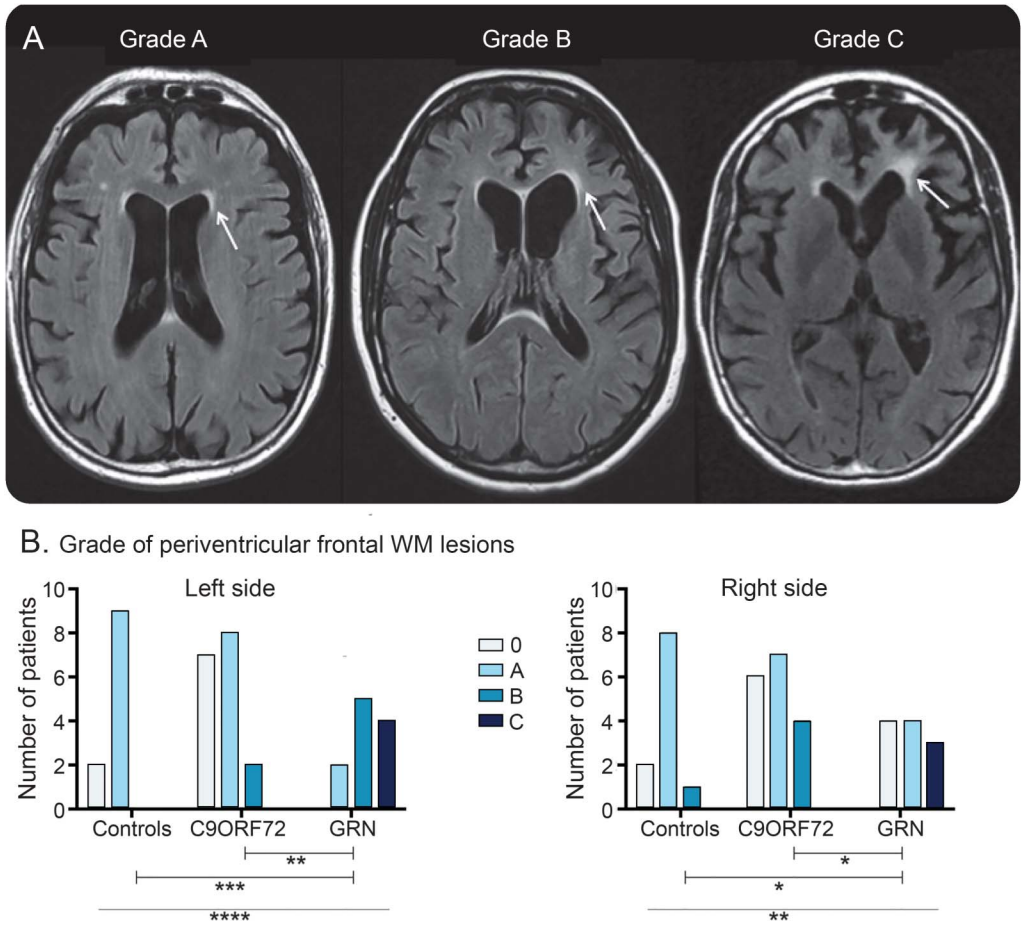
In *GRN* mutation carriers, the presence of grade C WM lesions on the left side was associated with a higher degree of left frontal atrophy ($p = 0.003$, Mann-Whitney test) but not with longer disease duration ($p = 0.082$, Mann-Whitney test). No significant result was observed for the right side, where WM lesions were less frequent.

Discussion. Previous reports have shown that some FTLD cases with *GRN* mutation present with marked FLAIR hyperintensities in the WM.[1–3,6] Here we extended these findings by showing that these WM lesions are frequent: 45% (5/11) of *GRN* mutation carriers had extensive frontal WM lesions (grade C) in the absence of noteworthy cardiovascular risk factors. These WM lesions were atypical for common cerebral small vessel disease because they extended toward the subcortical WM (figure) and were associated with a higher degree of left frontal atrophy. They were not associated with longer disease duration; thus, they may be a consequence of a faster atrophy process than in the other patients. Of note, the patient excluded from the study because of cardiovascular risk factors had only grade A WM lesions in the frontal lobes.

It is interesting that both *GRN* and *C9ORF72* mutation carriers are likely to have underlying FTLD-TDP43 pathology. This suggests that gene effects can exceed lesion effects in the phenotypical expression of

Supplemental data at Neurology.org/ng

Figure Visual score for the characterization of frontal WM lesions on FLAIR images



(A) Grade A: minor fluid-attenuated inversion recovery (FLAIR) hyperintensities, <4 mm thick, limited to the periventricular area, no extension into the deep and subcortical white matter (WM). Grade B: moderate FLAIR hyperintensities, <6 mm thick, affecting the periventricular and deep WM, no extension into the subcortical WM. Grade C: marked FLAIR hyperintensities, >6 mm thick, affecting periventricular, deep, and subcortical WM. (B) Frontal WM lesions were significantly different between groups on the left side ($p < 0.0001$, Kruskal-Wallis test) and on the right side ($p = 0.007$, Kruskal-Wallis test). Dunn post hoc tests showed statistically significant differences between the *GRN* group and controls and between the *GRN* group and the *C9ORF72* group for the left and right side.

FTLD. The progranulin protein is normally expressed not only in neurons but also in activated microglia, astrocytes, and oligodendroglia and plays a role in inflammation.[7] Histopathologic studies of the WM in *GRN* mutation carriers have reported microglial activation in the areas of abnormal WM on MRI.[2] These results favor the hypothesis of a specific vulnerability of the WM to granulin haploinsufficiency.

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