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White matter hyperintensities in progranulin-associated frontotemporal dementia – a longitudinal GENFI study

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Highlight:

White matter hyperintensities (WMH) accumulate over time in progranulin mutation carriers
WMH in GRN mutation carriers are associated with GM atrophy
WMH in GRN mutation carriers are associated with executive dysfunction
WMH load is variable across GRN mutation carriers

Main title

White matter hyperintensities in progranulin-associated frontotemporal dementia – a longitudinal GENFI study

Running title

WMH in *GRN* FTD

Authors

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The cross-sectional finding of increased WMH in the symptomatic *GRN* group within periventricular and medial regions, particularly within the frontal and occipital lobes is consistent with prior studies (Caroppo et al., 2014; Kelley et al., 2009) including a previous smaller study in the GENFI cohort (Sudre et al., 2017a). However, this study extends those findings to show differences within the presymptomatic cohort, where significant differences were found in the periventricular region and occipital lobes. Despite these findings, there remains large variability within the *GRN* population ð when classified into three groups of increasing severity, 25% of cases still have none or only mild WMH during the symptomatic phase, whilst 9% of the presymptomatic group already have severe WMH involvement.

A variable rate of longitudinal accrual of WMH was found in the *GRN* population, with the most significant increase in the medial region, suggesting a spread of WMH from initial periventricular regions outwards towards the cortex over time.

Forthcoming trials of disease-modifying therapy in *GRN* mutation carriers will require robust outcome measures. The presence of WMH cross-sectionally in only a subset of *GRN* mutation carriers and the variable accrual rate of WMH over time seems to preclude WMH volumes as being a global outcome measure across all participants (with the confidence intervals of calculated sample sizes being wide, and the upper limit extremely large). However, it may be possible to use WMH as markers within individual patients, and further work will be needed to investigate longitudinal changes over a longer period within the defined subset of *GRN* mutation carriers with WMH.

Frontal GM atrophy was found to be associated with frontal, periventricular and medial lesion load in the *GRN* mutation carriers but no such relationship could be found in the controls. Moreover, a longitudinal association between decreased baseline frontal GM volume and increased rate of WMH accrual in the frontal, periventricular and medial regions was seen. These findings are consistent with prior studies (Ameur et al., 2016; Caroppo et al., 2014; Kelley et al., 2009), and could be interpreted as

Wallerian degeneration (McAleese et al., 2017, 2015) involving a fronto-striatal circuit previously implicated in FTD (Looi et al., 2012). Notably, patients with *GRN* mutations have early striatal GM volume loss also (Rohrer et al., 2015a). The clinical relevance of such findings may well be the known association of *GRN* mutations with parkinsonism (including corticobasal syndrome) (Möller et al., 2015; van Swieten and Heutink, 2008), and further investigation of the association between WMH and extrapyramidal symptoms will be important.

The clinical outcome of increased WMH burden appears to be worse executive function and slower information processing, with a significant association seen with performance on the Digit Span backwards and Digit Symbol test. This is consistent with studies in other conditions where WMH predominantly affect anterior areas of the brain (Kennedy and Raz, 2009). Prior neuroimaging studies of FTD have associated executive dysfunction with frontal cortical GM disease (Rosen et al., 2002) but the current study suggests that such cognitive deficits in *GRN* mutation carriers are likely to be due to a complex combination of GM and WM disease.

The association of NfL concentration with WMH burden is perhaps unsurprising as NfL is often felt to be a generic marker of axonal (and therefore WM) damage. However, NfL can be increased in FTD in the absence of WMH, and the increase of NfL in the *GRN* population is therefore likely to be a function of both WM tract disease not seen on T1 and T2 MR imaging and WMH. Future multimodal studies combining T1, T2 and diffusion tensor imaging will be helpful to investigate this further.

The trend towards an association between GFAP concentration and WM lesion load is consistent with a recent pathological study of WMH in a *GRN* carrier that showed a strong association with the presence of astrogliosis (Woollacott *et al,* 2018). However there was only a weak relationship both cross-sectionally and longitudinally in our study and further work is required to better understand the role of GFAP and astrogliosis in the pathophysiology of WMH in *GRN* mutation carriers.

The risk genotype (TT) of the rs1990622 *TMEM106B* polymorphism was seen to be associated with an overall acceleration of WMH accrual over time in the *GRN* population but not in the control group. TMEM106B appears to regulate progranulin levels and disease penetrance in *GRN* mutation carriers (Finch et al., 2011), and the presence of the risk genotype is associated with lower GM volume (Harding et al., 2017) and impaired functional connectivity in the brain (Premi et al., 2017). This study adds to the knowledge about the role of *TMEM106B* in *GRN* mutation carriers and further work is needed to understand how the presence of the risk genotype leads to an increased accrual of WMH.

The underlying nature of the WMH in *GRN* mutation carriers has yet to be determined, although prior imaging and neuropathological work suggests that the lesions are not likely to be vascular (Sudre et al., 2017a; Woollacott et al., 2018) despite a relationship of progranulin with systemic metabolic disease (Nguyen et al., 2013), but instead are potentially inflammatory, with evidence of regional microglial dysfunction (Woollacott et al., 2018; Sakae et al., 2019). Recent studies suggest that lysosomal dysfunction within microglia is a key pathophysiological mechanism in *GRN* mutation carriers (Götzl et al., 2018), and that this is associated with *TMEM106B* function (Klein et al., 2017), hence providing a link to the findings in this study of a relationship between WMH and the *TMEM106B* risk genotype.

Apart from the fact that T2-weighted imaging may not be the optimal sequence of choice to segment WMH (including increased difficulty in segmentation at the ventricular border and the issue of jointly enlarged perivascular spaces and WMH), limitations of the study may include the relatively limited number of longitudinal cases available for analysis. However further data freezes within the GENFI study will allow larger longitudinal analyses to be performed in the future.

In order to further validate the hypothesis of Wallerian degeneration linking GM loss and WM lesions, the longitudinal evolution of diffusion tensor imaging metrics on the tracts impacted by lesions will be useful to investigate. Additionally, recent studies have highlighted the role of neuroinflammation and microglial activation in *GRN* mutation carriers, and particularly an

association of abnormal, dystrophic microglia with WMH (Woollacott et al., 2018): it will therefore be important to correlate WMH burden with measures of inflammation such as CSF markers or microglial PET imaging in future studies.

Competing interests

The authors declare no competing interests

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