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Longitudinal structural gray matter and white matter MRI changes in presymptomatic progranulin mutation carriers

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ABSTRACT

Introduction: Mutations in the progranulin (*GRN*) gene are a major source of inherited frontotemporal degeneration (FTD) spectrum disorders associated with TDP-43 proteinopathy. We use structural MRI to identify regions of baseline differences and longitudinal changes in gray matter (GM) and white matter (WM) in presymptomatic *GRN* mutation carriers (pGRN+) compared to young controls (yCTL).

Methods: Cognitively intact first-degree relatives of symptomatic GRN+ FTD patients with identified *GRN* mutations (pGRN+; $N = 11$, mean age = 41.4) and matched yCTL ($N = 11$, mean age = 53.6) were identified. They completed a MRI session with T1-weighted imaging to assess GM density (GMD) and diffusion-weighted imaging (DWI) to assess fractional anisotropy (FA). Participants completed a follow-up session with T1 and DWI imaging (pGRN+ mean interval 2.20 years; yCTL mean interval 3.27 years). Annualized changes of GMD and FA were also compared.

Results: Relative to yCTL, pGRN+ individuals displayed reduced GMD at baseline in bilateral orbitofrontal, insular, and anterior temporal cortices. pGRN+ also showed greater annualized GMD changes than yCTL at follow-up in right orbitofrontal and left occipital cortices. We also observed reduced FA at baseline in bilateral superior longitudinal fasciculus, left corticospinal tract, and frontal corpus callosum in pGRN+ relative to yCTL, and pGRN+ displayed greater annualized longitudinal FA change in right superior longitudinal fasciculus and frontal corpus callosum.

Conclusions: Longitudinal MRI provides evidence of progressive GM and WM changes in pGRN+ participants relative to yCTL. Structural MRI illustrates the natural history of presymptomatic GRN carriers, and may provide an endpoint during disease-modifying treatment trials for pGRN+ individuals at risk for FTD.

1. Introduction

Frontotemporal degeneration (FTD) is a progressive neurodegenerative condition that typically begins with behavioral or language problems (Seelaar et al., 2011). The disease primarily affects frontal and anterior temporal brain regions. Approximately 25% of FTD cases are inherited (Wood et al., 2013), and one of the most common familial causes of FTD is a mutation of the progranulin (*GRN*) gene (Baker et al., 2006; Cruts et al., 2006). *GRN* mutations are universally associated with TDP-43 pathology (Neumann et al., 2006) and thus carriers may be good candidates for disease-modifying treatment trials (Boxer and Boeve, 2007; Gass et al., 2012), particularly in presymptomatic mutation carriers where a successful trial may be preventive.

Widespread reductions in gray matter (GM) volume and thickness have previously been shown in symptomatic GRN carriers (GRN+) compared to controls in frontal and temporal regions typically compromised in FTD, as well as in regions less frequently implicated in FTD such as the parietal lobes and precuneus (Premi et al., 2014b; Rohrer et al., 2010; Whitwell et al., 2009, 2007). A longitudinal evaluation of GM atrophy showed more rapid changes across frontal, temporal,

Abbreviations: GRN, progranulin; pGRN+, presymptomatic progranulin mutation carriers; GRN+, symptomatic progranulin mutation carriers; yCTL, young healthy controls; eCTL, elderly healthy controls; FTD, frontotemporal degeneration; GM, gray matter; WM, white matter; GMD, gray matter density; FA, fractional anisotropy; DWI, diffusion-weighted imaging; RD, radial diffusivity; AD, axial diffusivity; MD, mean diffusivity; ROI, region of interest; BA, Brodmann area; SLF, superior longitudinal fasciculus; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; CST, corticospinal tract

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parietal, and even occipital regions in GRN+ individuals than sporadic FTD patients (Whitwell et al., 2015). Voxelwise studies of white matter (WM) in GRN+ cases of FTD have been examined less frequently, but extensive involvement of WM association fibers has been documented compared to healthy controls (Rohrer et al., 2010).

Prior cross-sectional structural and functional MRI imaging studies in presymptomatic *GRN* carriers (pGRN+) have identified differences in both GM and WM frontal and temporal regions (Borroni et al., 2012; Dopper et al., 2013; Pievani et al., 2014; Premi et al., 2014a). Yet, it remains to be shown that these changes are related to neurodegeneration rather than normal aging. Longitudinal studies looking at functional imaging have provided some evidence of presymptomic changes occurring in pGRN+ individuals in frontal, temporal, and parietal regions (Caroppo et al., 2015; Dopper et al., 2016). Changes observed in a longitudinal structural imaging study would provide some evidence that progression is due to neurodegeneration; one study has reported progressive atrophy in a temporal region in pGRN+ individuals (Caroppo et al., 2015), but this change was not compared to controls. Here, we provide novel evidence for longitudinal changes in brain structure derived from serial MRI imaging of pGRN+ individuals relative to controls. We hypothesized neurodegeneration in both GM and WM in pGRN+ at baseline, and greater annualized longitudinal changes relative to controls.

2. Materials and methods

2.1. Subjects

We identified symptomatic individuals with a *GRN* mutation (GRN+) from the Penn Frontotemporal Degeneration Center and Cognitive Neurology Clinic at the University of Pennsylvania ($N = 15$, 10 females) to be used as a symptomatic reference cohort for the pGRN+ comparisons. A board-certified neurologist with expertise in neurodegenerative conditions diagnosed these probands with an FTD-spectrum disease using published criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). The GRN+ cohort included different clinical presentations, including behavioral variant FTD (bvFTD; $N = 6$), corticobasal syndrome ($N = 4$), non-fluent/agrammatic primary progressive aphasia ($N = 3$), semantic variant primary progressive aphasia ($N = 1$), and Alzheimer's Disease ($N = 1$). To be included in this study, GRN+ patients had to have a T1-weighted MRI to assess GM density (GMD). A subset of these patients ($N = 9$, 5 females) also underwent a 30-directional diffusion-weighted imaging (DWI) sequence to assess fractional anisotropy (FA). A matched elderly healthy control group (eCTL; $N = 24$, 15 females) also underwent T1-weighted and 30-directional DWI MRI, though one was removed from the DWI analysis due to poor image quality due to artifact. Table 1 summarizes GRN+ and eCTL demographic information.

Table 1
Demographic characteristics of symptomatic progranulin mutation carriers (GRN+) and elderly controls (eCTL). The table displays the mean (standard deviation) of GRN+ and eCTL. Significant differences between GRN+ and eCTL are noted by * (two-sample *t*-tests, significance at $p < 0.05$).

	eCTL	GRN+
Number (female)	23 (15)	15 (10)
Age (years)	63.8 (7.37)	63.0 (6.62)
Education (years)	14.9 (2.26)	14.7 (3.83)
Symptomatic Disease Duration (years)	–	2.00 (1.07)
MMSE (max score = 30)*	29.2 (0.89)	19.0 (5.97)
Forward Digit Span*	7.40 (0.70)	5.67 (1.73)
Reverse Digit Span*	5.93 (1.10)	1.89 (1.62)
Boston Naming (max score = 30)*	28.2 (1.20)	17.4 (7.04)

Notes
1. Forward and reverse digit span and Boston naming test available for 9 GRN+.

First degree relatives of patients FTD were also recruited for research. These individuals were invited to participate in research that included MRI, neuropsychological testing, and genetic testing. For inclusion in the study, all of these individuals had to be cognitively normal, defined as no self-report of cognitive impairment and no reports of cognitive impairments by friends or family members, with a Clinical Dementia Rating (CDR) score of 0, and must have completed two MRI sessions that included a high resolution T1-weighted scan and a 30-directional DWI sequence. 11 individuals (7 females) that were first-degree relatives of symptomatic GRN+ patients had a mutation in *GRN* (pGRN+). We also recruited a matched young control group from the general population (yCTL; $N = 11$, 7 females). Subsets of the pGRN+ ($N = 1$) and yCTL ($N = 2$) had artifacts in their follow-up DWI scans and were thus excluded from the longitudinal WM analyses. No significant differences were found between pGRN+ and yCTL participants in demographic features, which included education, age, sex, or duration between scans (all $p > 0.05$). Also, no differences were found between pGRN+ and yCTL in baseline or follow-up neuropsychological testing performance (all $p > 0.05$), indicating that these individuals were truly without any evidence of disease. Table 2 summarizes demographic information and cognitive performance for presymptomatic cases. All participants completed a written informed consent procedure under a protocol approved by the Institutional Review Board convened at the University of Pennsylvania.

2.2. Genetic screening

DNA was extracted from peripheral blood following the manufacturer's protocols (Flexigene (Qiagen) or QuickGene DNA whole blood kit (Autogen)). Samples were tested for mutations in the entire *GRN* coding region using Sanger sequencing and/or targeted next generation sequencing (NGS) with a neurodegenerative disease-focused panel (multi neurodegenerative disease sequencing panel, MiND-Seq), that also tests for additional genes associated with FTD including *MAPT*, *VCP*, *CSF1R*, *TBK1*, *CHMP2B*, and *SQSTM1* (*C9orf72* expansion analysis was done separately) (Toledo et al., 2014; Wood et al., 2013). Sanger sequencing data were analyzed with Mutation Surveyor software (SoftGenetics, State College, PA) and alignment of sequence reads and variant calling from NGS were assessed by SureCall software (Agilent, Santa Clara, CA). Genetic screening revealed **11** asymptomatic participants with longitudinal MRI and a known pathogenic mutation of *GRN* associated with FTLD-TDP (Baker et al., 2006).

2.3. Image acquisition

All participants underwent a structural T1-weighted MPRAGE MRI acquired from a SIEMENS 3.0 T Trio scanner with an eight-channel coil using the following parameters: TR = 1620 ms; TE = 3 ms; 160 1.0 mm slices; flip angle = 15°; matrix = 192 × 256; in-plane resolution = 0.9766 mm × 0.9766 mm. In each session, all pGRN+ and yCTL participants also underwent a 30-directional DWI sequence, acquired using a single-shot, spin-echo, diffusion-weighted echo-planar imaging sequence with GRAPPA acceleration factor of 3. A subset of GRN+ patients were unable or unwilling to participate in the DWI portion of the protocol ($N = 6$). The diffusion sampling scheme consisted of either one or five images with $b = 0\ s/mm^2$, followed by measurements with 30 non-collinear/non-coplanar directions isotropically distributed in angular space ($b = 1000\ s/mm^2$), TR = 6700 ms, TE = 85 ms, slice thickness = 2.2 mm, and FOV 245 × 245 mm, reconstructed to 2.19 × 2.19 mm in-plane resolution.

2.4. Image preprocessing

2.4.1. Cross-sectional and baseline processing

To identify regions likely related to clinical disease and help validate our observations of MRI change in presymptomatic individuals, we