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Pattern of structural and functional brain abnormalities in asymptomatic granulin mutation carriers

Michela Pievani[a], Donata Paternicò[a], Luisa Benussi[b], Giuliano Binetti[b], Alberto Orlandini[c], Milena Cobelli[c], Silvia Magnaldi[c], Roberta Ghidoni[d], Giovanni B. Frisoni[a,e,*]

[a]*Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS Istituto Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy*
[b]*NeuroBioGen Lab—Memory Clinic, IRCCS Istituto Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy*
[c]*Neuroradiology and Angiology Unit, Fondazione Poliambulanza, Brescia, Italy*
[d]*Proteomics Unit, IRCCS Istituto Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy*
[e]*Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland*

Abstract

Background: To investigate the patterns of brain atrophy, white matter (WM) tract changes, and functional connectivity (FC) abnormalities in asymptomatic granulin (*GRN*) mutation carriers.
Methods: Ten cognitively normal subjects (five mutation carriers, *GRN*+; years to estimated disease onset: 12 ± 7; five mutation noncarriers, *GRN*−) underwent a clinical and imaging (structural, diffusion tensor, and resting-state functional magnetic resonance imaging) assessment. Brain atrophy was measured with cortical thickness analysis, WM abnormalities with tract-based spatial statistics, and FC with independent component analysis.
Results: *GRN*+ showed smaller cortical thickness than *GRN*− in the right orbitofrontal and precentral gyrus and left rostral middle frontal gyrus. WM tracts abnormalities were limited to increased axial diffusivity in the right cingulum, superior longitudinal fasciculus, and corticospinal tract. There were no differences in FC of resting-state networks.
Conclusion: Brain atrophy and WM tract abnormalities in frontal-parietal circuits can be detected at least a decade before the estimated symptom onset in asymptomatic mutation carriers.

Keywords: FTLD; Progranulin; Magnetic resonance imaging; Cortical thickness; Diffusion tensor; Resting-state functional MRI

1. Introduction

Frontotemporal lobar degeneration (FTLD) denotes a large group of neurodegenerative conditions characterized by frontal and temporal symptoms and atrophy. FTLD patients have a strong familial component with between 20% and 50% of all cases reporting a familial history for the disease. Three genetic mutations have been identified to date as major causes for the disease: mutations in the gene encoding the granulin protein (*GRN*), the microtubule associated tau protein (*MAPT*), and, recently, the chromosome 9 open reading frame 72 (*C9orf72*) [1]. Prevalence estimates vary according to geographic differences [1]. In northern Italy, *GRN* mutations are among the most common genetic causes of FTLD, whereas *MAPT* mutations are relatively less frequent [2–5]. All *GRN* mutations identified thus far cause disease through a uniform disease mechanism: the loss of functional progranulin or haploinsufficiency [6,7]. Progranulin and granulins are secreted growth factors involved in multiple biological functions, including neuronal development and synaptic maintenance. The loss of progranulin in patients carrying pathogenic *GRN* null mutations is thus thought to increase susceptibility to neuronal death [7]. Because FTLD mutations are inherited in an autosomal dominant manner and in *GRN* null mutation carriers the shortage of progranulin precedes clinical

*Corresponding author. Tel.: +39-030-3501361; Fax: +39-030-3501592.
E-mail address: gfrisoni@fatebenefratelli.it

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symptoms [8–11], asymptomatic members of families with *GRN* mutations offer a unique possibility to investigate early pathologic changes and identify disease biomarkers.

Recent evidence from familial Alzheimer's disease has shown that the pathologic changes start approximately 25 years before the onset of clinical symptoms, and brain atrophy occurs approximately 15 years before clinical onset [12]. In familial FTLD, a similar pattern of early pathology is likely to occur; however, evidence to date is scarce and mostly limited to symptomatic cases. In FTLD patients carrying a *GRN* mutation, the main pathologic signatures on magnetic resonance imaging are an involvement of the fronto-temporo-parietal circuits, with prominent parietal and asymmetric atrophy [13–15], impaired connectivity in long-distance intrahemispheric tracts [13], and salience network disruption [16]. The involvement of the parietal regions seems to be unique to *GRN* mutations compared with mutations in *MAPT* or *C9orf72* [17,18]. Which brain abnormalities occur first (atrophy, structural, or functional disconnection) and how many years before the clinical symptoms these changes occur remains to be confirmed. One previous study assessed atrophy and functional connectivity changes in asymptomatic *GRN* mutation carriers, reporting increased salience network connectivity with no brain atrophy [16]. In another study by the same group, early impairment of long-distance association tracts was reported [19], consistently with the white matter (WM) abnormalities observed in full-blown FTLD [20]. Although promising, these findings have been replicated by others only in part [21]. Moreover, only one study has assessed brain atrophy, functional disconnection, and WM abnormalities together in the same patients [21].

The aim of this study was to comprehensively investigate the pattern of brain atrophy, WM tract abnormalities, and functional connectivity abnormalities in asymptomatic *GRN* mutation carriers. We hypothesized that structural and functional abnormalities might be detected in asymptomatic subjects along the circuits typically affected in symptomatic FTLD.

2. Methods

2.1. Subjects

Subjects were recruited at the Istituto di Ricovero e Cura a Carattere Scientifico Centro S. Giovanni di Dio Fatebenefratelli (www.irccs-fatebenefratelli.it) from five unrelated *GRN*-positive pedigrees identified in northern Italy. Four families carried the *GRN* p.Leu271LeufsX10 mutation [22], and one carried the *GRN* p.Thr278SerfsX7 mutation [23]. The phenotypes of these families were behavioral-variant frontotemporal dementia (bv FTD; n = 2), primary progressive aphasia (PPA, n = 1), and FTD with motor neuron disease (n = 1) for the four pedigrees with the *GRN* p.Leu271LeufsX10 mutation, and PPA for the family with the p.Thr278SerfsX7 mutation. Age of onset in these pedigrees was on average 61 ± 4 years, ranging from 49 to 66 years. Subjects were included if they (1) were screened for the presence or absence of *GRN* mutations, (2) were cognitively normal, and (3) underwent magnetic resonance imaging (MRI). Ten unaffected family members fulfilled these criteria: five screened positive for a *GRN* mutation (*GRN*+, 4 with the *GRN* p.Leu271LeufsX10 mutation and 1 with the *GRN* p.Thr278SerfsX7 mutation), and the remaining five screened negative for *GRN* mutations and served as a control group (*GRN*−). Among *GRN*+ subjects, two p.Leu271LeufsX10 mutation carriers were from the same family (PPA phenotype), and the remaining three were from three unrelated pedigrees (1 FTD with motor neuron disease, 1 PPA, 1 bv FTD). Plasma progranulin levels were 23 ± 10 ng/mL in *GRN*+ and 94 ± 32 ng/mL in *GRN*− ($P < .05$; Table 1).

Table 1
Demographic and cognitive features of asymptomatic progranulin mutation carriers (*GRN*+) and control nonmutation carriers (*GRN*−)

	Whole sample	*GRN*− (n = 5)	*GRN*+ (n = 5)	*P*	P_{np}
Progranulin levels (ng/mL)*	50 ± 41 [11–127]	94 ± 32	23 ± 10	.003	.03
Age (y)	46 ± 12 [28–63]	46 ± 15	45 ± 10	.88	.84
Gender (women)	8	5	3	.44	.44
Education (y)	10 ± 3 [5–13]	9 ± 4	11 ± 3	.46	.54
Time to estimated onset (y)	—	—	12 ± 7	—	—
MMSE	29 ± 1 [26–30]	29 ± 1	29 ± 2	.68	1.00
Rey-Osterrieth Figure Copy	31 ± 6 [22–36]	33 ± 6	30 ± 5	.47	.11
Rey-Osterrieth Figure Copy Recall	15 ± 6 [10–25]	16 ± 5	14 ± 7	.71	.73
Boston Naming Test	28.5 ± 1 [27–30]	28.5 ± 2	28.5 ± 1	1.00	1.00
Category verbal fluency	45 ± 8 [35–60]	41 ± 3	49 ± 11	.27	.29
Letter verbal fluency	34 ± 9 [22–48]	31 ± 6	38 ± 12	.37	.41
Token Test	34 ± 2 [29–35]	33.5 ± 3	34 ± 1	.61	.89
Rey's Word List Immediate Recall	57 ± 9 [40–70]	51 ± 9	62 ± 7	.15	.23
Rey's Word List Delayed Recall	12 ± 2 [8–15]	12 ± 3	13 ± 2	.56	.63
Trail Making Test Part A	50 ± 26 [30–101]	48 ± 23	53 ± 33	.83	.91
Trail Making Test Part B	116 ± 49 [62–221]	116 ± 63	115 ± 33	.98	.56

NOTE. Numbers denote mean ± SD [range], or frequency. *P* denotes significance on two-tailed Student's *t* test for continuous variables or $\chi 2$ test for dichotomous variables. P_{np}, significance on two-tailed Mann-Whitney *U* test. MMSE, Mini-Mental State Examination.

*Plasma progranulin levels were available in all mutation carriers and in three noncarriers.