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Disease-related cortical thinning in presymptomatic granulin mutation carriers

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ABSTRACT

Mutations in the *granulin* gene (*GRN*) cause familial frontotemporal dementia. Understanding the structural brain changes in presymptomatic *GRN* carriers would enforce the use of neuroimaging biomarkers for early diagnosis and monitoring. We studied 100 presymptomatic *GRN* mutation carriers and 94 noncarriers from the Genetic Frontotemporal dementia initiative (GENFI), with MRI structural images. We analyzed 3T MRI structural images using the FreeSurfer pipeline to calculate the whole brain cortical thickness (CTh) for each subject. We also perform a vertex-wise general linear model to assess differences between groups in the relationship between CTh and diverse covariables as gender, age, the estimated years to onset and education. We also explored differences according to *TMEM106B* genotype, a possible disease modifier. Whole brain CTh did not differ between carriers and noncarriers. Both groups showed age-related cortical thinning. The group-by-age interaction analysis showed that this age-related cortical thinning was significantly greater in *GRN* carriers in the left superior frontal cortex. *TMEM106B* did not significantly influence the age-related cortical thinning. Our results validate and expand previous findings suggesting an increased CTh loss associated with age and estimated proximity to symptoms onset in *GRN* carriers, even before the disease onset.

1. Introduction

Frontotemporal dementia (FTD) is a clinically, genetically and pathologically heterogeneous group of neurodegenerative diseases characterized by behavioral and language impairment. FTD is a highly heritable disorder, with mutations in several genes causing genetic forms of the disease. Mutations in the *progranulin* (*GRN)* gene were identified in 2006 as a cause of familial FTD with TAR-DNA binding protein 43 (TDP-43) inclusions (Baker et al., 2006; Cruts et al., 2006). The prevalence of *GRN* mutations has been estimated at 6% of all FTD patients and 20% of familial FTD (Cruts and Van Broeckhoven, 2008). The majority of FTD due to *GRN* mutations patients present a behavioral variant FTD, non-fluent primary progressive aphasia or corticobasal syndrome (Moore et al., 2019).

In 2010, a genome-wide association study revealed *transmembrane protein 106B* (*TMEM106B)* gene as a risk factor for FTD with TDP-43 inclusions (Van Deerlin et al., 2010). Further studies had replicated these findings, showing an extremely low presence of the *TMEM106B* minor allele in homozygosis in *GRN* patients, indicating that individuals who are homozygous for the minor *TMEM106B* allele are less likely to develop symptoms (Finch et al., 2011; Nicholson and Rademakers, 2016).

Previous work using structural MRI revealed that symptomatic *GRN* mutation carriers typically show a widespread but asymmetric pattern of grey matter (GM) loss, affecting frontal, temporal and parietal lobes (Beck et al., 2008; Fumagalli et al., 2018; Whitwell et al., 2009). Studies in presymptomatic *GRN* mutations carriers have shown divergent results, with many of them reporting no significant brain structural differences compared with noncarriers (Borroni et al., 2012, 2008; Caroppo et al., 2015; Cash et al., 2018; Olm et al., 2018; Panman et al., 2019; Pievani et al., 2014; Rohrer et al., 2015). *TMEM106B* variants have also been studied in the general population using neuroimaging, with the risk allele being related to reduced volume of the left temporal lobe in non-demented subjects (Adams et al., 2014). In this line, and complementing the structural findings, Premi et. al. used functional MRI and found that, in *GRN* carriers, the *TMEM106B* risk haplotype was associated with decreased functional connectivity in the left frontoparietal network (Premi et al., 2014).

In a previous cross-sectional study with a limited number of subjects, we observed that presymptomatic *GRN* mutation carriers presented greater loss of cortical thickness (CTh) by age in temporal areas compared to noncarriers (Moreno et al., 2013). Here, we aimed to expand these previous findings by investigating the change in CTh in a much larger cohort of presymptomatic mutation carriers using data from the Genetic Frontotemporal Dementia Initiative (GENFI). We also aimed to investigate the potential influence of the *TMEM106B* genotype in the grey matter loss in *GRN* carriers.

2. Methods

2.1. Participants

We analyzed cross-sectional data from the GENFI study (Rohrer et al., 2015), Data Freeze 3. The GENFI cohort includes subjects at risk of genetic FTD, from centres across Europe and Canada (https://www.genfi.org/). Subjects in the cohort undergo a standardized clinical and neuropsychological assessment as well as an MRI exam once a year (Rohrer et al., 2013). Our work included the baseline data from 100 presymptomatic mutation carriers and 94 noncarriers from 54 different families. For each subject, sex, age, estimated years to onset (EYO) and education were obtained from the GENFI database. The EYO was computed considering the difference between the subject's age and the average familial age of symptom onset. Asymptomatic status was ascertained based on relative's interview, neurological examination and normality on behavioral scales and neuropsychological tests. Local ethics committees at each site approved the study and all participants provided written informed consent.

2.2. TMEM106B genetic analysis

TMEM106B rs1990622 (C/T) single nucleotide polymorphism was performed according to standard procedures (Premi et al., 2014) in 90 subjects: 46 presymptomatic *GRN* carriers and 44 noncarriers.

2.3. Demographic and clinical statistical analysis

Differences in the clinical and demographic data between carriers and presymptomatic carriers were assessed using *t*-test for continuous variables and chi-squared test was used for dichotomous data. Differences in demographics between *TMEM106B* genotypes were assessed with non-parametric tests (Fisher Test for dichotomous data and Kruskall-Wallis Test for continuous data).

2.4. Image acquisition and processing

Participants underwent a 1.1-mm isotropic resolution volumetric T1 MR imaging on a 3 T using the sequences defined within the GENFI consortium.

MRI images of all subjects were downloaded from GENFI database and processed using FreeSurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu/), with the main goal of computing individual CTh surface maps. Briefly, the FreeSurfer pipeline includes skull stripping (Ségonne et al., 2004), segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2004, 2002), tessellation of boundaries, and definition of the transition between tissue classes. Then, CTh is calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex (Dale et al.,

1999; Fischl and Dale, 2000).

Individual CTh maps were visually inspected to detect and correct processing errors. From an initial sample of 114 presymptomatic mutation carriers and 101 noncarriers, 21 subjects were excluded due to bad reconstruction or other FreeSurfer processing errors, resulting in the final sample of 100 presymptomatic carriers and 94 noncarriers. Surface maps were registered to the standard average space and smoothed with a Full Width at Half Maximum (FWHM) of 15 mm.

2.5. Image-based statistics

We first obtained whole brain CTh for each subject, calculated as the average CTh across all vertices (i.e., weighted average between the two hemispheres). This measure was correlated using Pearson's coefficient with age to investigate global age-related trajectories in the two groups. Linear and non-linear regression models were explored in the whole group as showed in the Supplementary material to determine the association between the whole CTh and age (Supplementary material). Due the lack of difference between linear and non-linear models, we used vertex-wise general linear models as implemented in FreeSurfer to test differences between carriers and noncarriers as well as interaction with age at the regional level. We added sex, education and the scanner used as covariates. Homoscedasticity of the samples were assessed by the Non-Constant Variance Test. In addition to chronological age, we also assessed the effect on CTh of the EYO. All maps were corrected for multiple comparisons using precomputed Monte Carlo permutations with a significance threshold of $p < 0.05$ (for both thresholding and cluster significance), as implemented in Freesurfer.

To study whether there were differences in asymptomatic carriers as they approached the predicted symptoms onset, we repeated the group comparison analysis (i.e., carriers vs non-carriers) using only the subgroup of subjects that were closer to the disease onset (i.e. those with EYO > -10 years).

Finally, we repeated the multiple linear regression adding the *TMEM106B* genotype as covariable. For this analysis, we assess the ROIs found significant different in the previous analyses.

3. Results

3.1. Demographic and genetic results

The demographic and genetic data of the 194 subjects are described in Table 1. The mean age at onset of the 54 different families included was 60.1 years (range 43 – 74.5 years). There were no differences in age, EYO, sex or education between groups. On average, presymptomatic mutation carriers presented an EYO of −13.0 years. No significant differences were found in *TMEM106B* haplotypes between groups. In both groups, the homozygosity for the protective genotype (C/C) were rare (6.8% in noncarriers carriers and 6.2% in presymptomatic carriers). No differences in gender, age, EYO or education were found between the different *TMEM106B* genotypes.

Table 1
Demographic characteristics and *TMEM106B* genotype. EYO: Estimated Years to Onset, SD: standard deviation; ns: not significant, *TMEM106B*: *transmembrane protein 106B*.

	Noncarriers n = 94	*GRN* presymptomatic carriers n = 100	Group differences p value
Age, years mean (SD)	47.5 (13.2)	46.8 (12.2)	0.595
EYO, years mean (SD)	−13.2 (14.9)	−13.0 (12.2)	0.967
Sex male/female	51/43	65/35	0.141
Education, years mean (SD)	14.2 (3.8)	14.6 (3.6)	0.658
TMEM106B (rs1990622)	**n = 44**	**n = 46**	
C/C (%)	3 (6.8%)	3 (6.5%)	0.889
C/T (%)	27 (61.4%)	26 (56.5%)	
T/T (%)	14 (31.8%)	17 (37.0%)	

3.2. Group differences in cortical thickness

There were no differences in CTh at the group level when comparing presymptomatic mutation carriers and noncarriers groups, neither with global measures nor with vertex-wise analyses. We hypothesized that this lack of difference might be consequence of the inclusion of subjects far from the predicted age at onset, and we also performed the whole-brain vertex-wise analysis between carriers and noncarriers in the subgroup of subjects nearest to the expected onset (EYO > -10), but no significant differences arose.

3.3. Correlation between cortical thickness and age

When we evaluated the CTh correlation with age at the whole-brain level, both presymptomatic mutation carriers and noncarriers showed a pattern of cortical thinning associated with age ($r = -0.59$ vs $r = -0.53$, both significant with $p < 0.001$), but no significant differences were observed differences between them at the whole brain level ($p = 0.272$) (Fig. 1).

3.4. Vertex-wise general linear models

When comparing carriers and noncarriers at the vertex-wise level with an interaction model, we identified a cluster with significant results (corrected $p < 0.05$) in the left superior frontal cortex (Fig. 2A). Age, gender, education and scanner were included as covariates. When studying the trajectories separately for each group within the significant ROI, we found that presymptomatic carriers showed a significant negative correlation between age and CTh ($r = -0.57$, $p < 0.001$), while noncarriers did not ($r = -0.12$, $p = 0.265$) (Fig. 2B). Additionally, we performed a multiple linear regression model within the ROI to quantify the effect of age education and gender into this result. Only Age and Age × group interaction were significant ($p < 0.001$, see Table 2).

3.5. Correlations between cortical thickness and EYO

Due to the presence of different *GRN* mutations that may present different ages of onset, we repeated the interaction analysis using EYO instead of actual age. We identified a cluster with significant differences between carriers and noncarriers (corrected $p < 0.05$) covering the right temporal cortex, the banks of superior temporal sulcus, the inferiorparietal and the supramarginal gyrus. It is noticeable that these regions also appeared in the analysis with age, however they did not survive multiple comparisons. Again, we performed multiple linear regression models to predict the ROI-CTh of these areas considering EYO (instead the age), we found similar results, with presymptomatic carriers presenting significant higher CTh loss by age than noncarriers ($p < 0.01$). Fig. 3 shows the correlation between CTh and EYO in both groups. ($r = -0.65$ for carriers vs $r = -0.33$ for noncarreirs, $p < 0.01$) (Fig. 3).

3.6. Influence of the TMEM106B genotype in the CTh – Age relationship

We did not find significant results at the vertex-wise level for the *TMEM106B* analyses for any of the comparisons tested. Therefore, we performed a hypothesis-driven study by focusing on the region that resulted significant in the *age* × *group* interaction. We divided the *GRN* carriers in groups according their *TMEM106B* genotype we found a significant negative correlation in the T/C carriers ($r = -0.52$, $p < 0.01$) and the T/T carriers ($r = -0.47$, $p < 0.05$), but not in the three subjects with the C/C genotype ($r = -0.365$, $p = 0.762$; Fig. 4). Only the correlation of the T/C carriers was significant and showed statistical

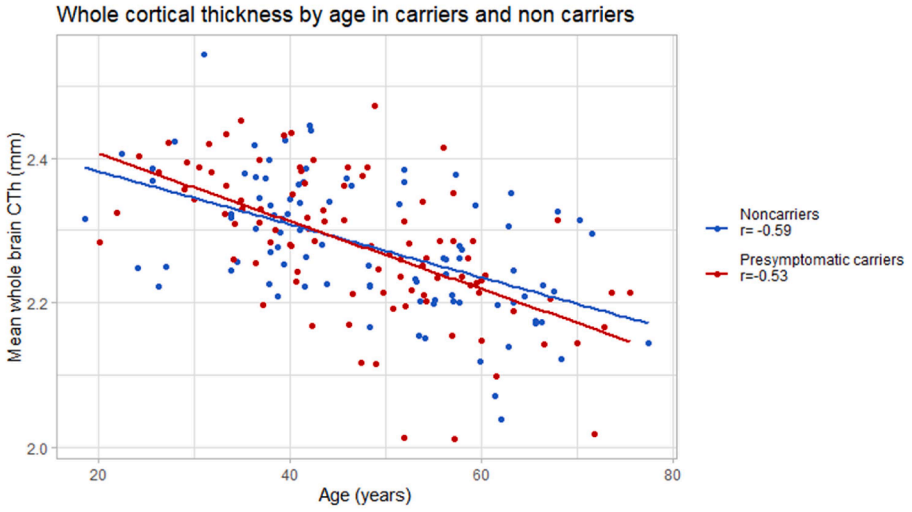

Fig. 1. Scatter plot showing correlation between whole CTh and age in presymptomatic *GRN* carriers (red) and noncarriers (blue). No statistical differences between trajectories were found. CTh: Cortical Thickness. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

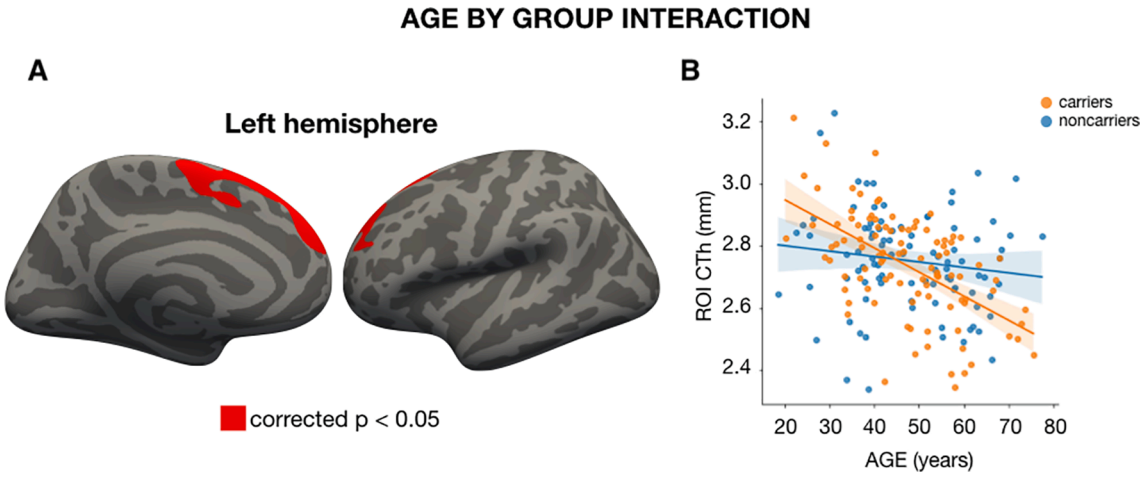

Fig. 2. Relationship between CTh and age in the selected area of the cortex where significant differences between carriers and noncarriers where found: A) Brain maps showing the area with statistical differences between presymptomatic carriers and noncarriers ($p < 0.05$). B) Scatter plot showing relationship between CTh and age in presymptomatic *GRN* carriers (red) and noncarriers (blue) in the selected area. Lines represent estimated linear regression models for both groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Multiple linear regression model to predict CTh based on the presence of GRN mutation (presymptomatic carriers vs noncarriers) and age. Sex and education were added as covariates.

	β (95% CI)	t value	p value
Intercept	3.021 (2.857, 3.185)	36.82	<0.001
GRN	0.019 (−0.025, 0.063)	0.85	0.393
Noncarriers vs *carriers*			
Age (years)	−0.008 (−0.010, −0.005	−6.03	**<0.001**
Education (years)	0.050 (−0.001, 0.011)	1.68	0.094
Gender	−0.001 (−0.046, 0.043)	−0–05	0.956
Male vs female			
Age × *GRN*	0.006 (0.003, 0.010)	3.50	**<0.001**

differences with the noncarriers group ($p < 0.05$). When we added the *TMEM106B* genotype as covariate to the multiple linear regression analysis we did not find any influence of this over the CTh, neither for presymptomatic carriers nor the noncarriers.

4. Discussion

In this study, we used data from the GENFI cohort to evaluate CTh in presymptomatic *GRN* mutation carriers. Although we did not find differences between carriers and noncarriers at the group-wise comparison, we found differences in the influence of aging and estimated years to onset in CTh, suggesting a greater cortical loss in presymptomatic carriers as they approach the clinical onset.

Several cross-sectional and longitudinal studies have evaluated GM loss in presymptomatic *GRN* mutation carriers with different methodologies, with partially divergent results. Our study, as most previous cross-sectional studies using structural MRI, did not find gray matter cortical thickness differences between presymtomatic *GRN* mutation carriers and controls (Borroni et al., 2012, 2008; Caroppo et al., 2015; Cash et al., 2018; Dopper et al., 2013; Fumagalli et al., 2018; Moreno et al., 2013; Panman et al., 2019). By contrast, few studies found gray matter atrophy pattern in presymptomatic carriers: Pievani and colleagues found greater GM loss in frontal areas, (Pievani et al., 2014) while Rohrer et. al. found significant differences between carriers and

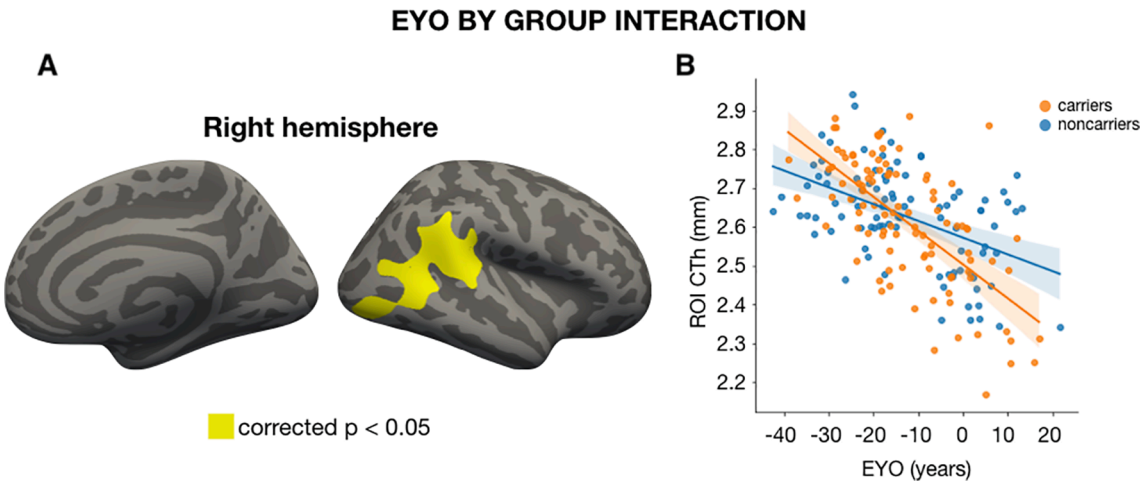

Fig. 3. Relationship between CTh and EYO: (A) Brain maps showing areas with statistical differences between carriers and noncarriers. B) Scatter plot illustrates the relationship between CTh and EYO in carriers and noncarriers. The X-axis represents the EYO. The Y-axis represents the mean CTh of the ROI covering all areas with significant differences between carriers and noncarriers. CTh: Cortical Thickness; EYO: estimated years to onset; ROI: Region of Interest.

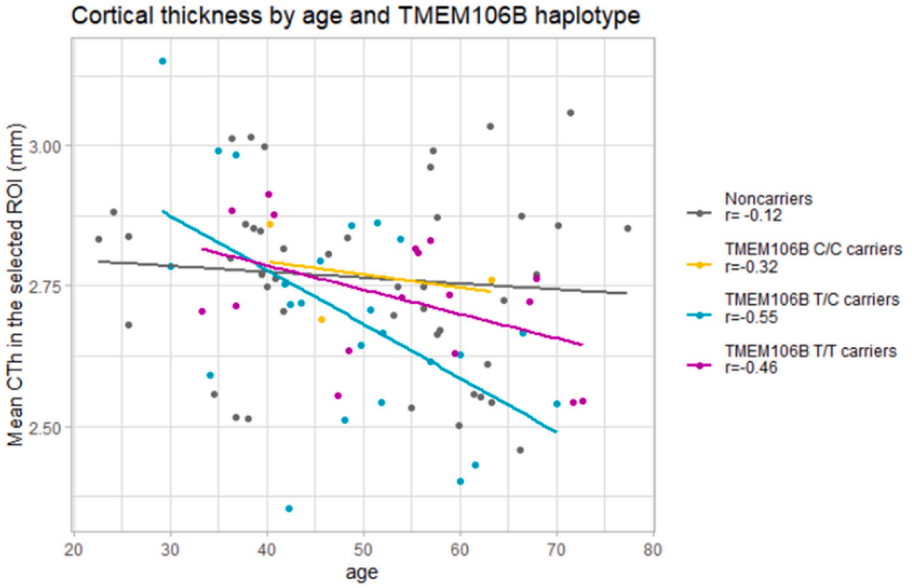

Fig. 4. Scatter plot showing relationship between CTh and age in *GRN* carriers according their *TMEM106B* genotype and noncarriers in the left superior frontal cortex.

noncarriers in the insula 15 years before the expected onset, and in the temporal and parietal lobes 10 years before the expected onset (Rohrer et al., 2015). These discrepancies in the quantification of GM loss in presymptomatic *GRN* mutation carriers differ from the extensive GM atrophy observed in symptomatic mutation carriers, even with a visual inspection. Several explanations have been proposed to explain this divergence of results. First, in a group cross-sectional comparison, subjects far from symptom onset are mixed with subjects close to disease onset; if CTh loss in *GRN* mutation carriers accelerates around the time of symptoms onset, mixing subjects at different intervals from symptom onset could cancel any apparent differences with noncarriers. In addition, the asymmetric pattern of atrophy in *GRN* mutation carriers might limit the differences in group-wise neuroimaging analyses.

In a previous study, in a sample of 13 presymptomatic *GRN* mutation carriers we observed that presymptomatic carriers presented greater age-related cortical thinning in the temporal areas when compared with controls (Moreno et al., 2013). In the present study, we expand these previous results in a much larger cohort of subjects at risk of FTD due to mutations in *GRN*. We found that both, presymptomatic *GRN* carriers and noncarriers showed a negative correlation of their CTh with age, with older subjects presenting lesser CTh. With the interaction analysis, we found a group-by-age effect in the left superior frontal cortex. In addition, the results of the multiple linear model of our study showed that, in this area, the presymptomatic carriers showed significantly greater loss of CTh with age than noncarriers. It might suggest that presymtomatic *GRN* carriers suffer a greater neuronal loss in this area due to neurodegeneration rather than normal aging. This is an area particularly affected in symptomatic patients (Cash et al., 2018) that have also been found to have increased rates of atrophy in longitudinal studies with presymptomatic carriers (Caroppo et al., 2015; Chen et al., 2019).

Recent work suggests that EYO has limited value in *GRN* families, due to a weak correlation between the individual age at onset and family age at onset (Moore et al., 2019) but better predictive markers of the disease age of onset are still lacking. Thus, as the present sample includes different *GRN* mutations, we also investigate the effect of EYO in

CTh in addition to the effect of the chronological age. When we study the correlation between CTh values and EYO, we found significant differences between presymptomatic *GRN* carriers and noncarriers in the right supramarginal gyrus and the banks of the rightsuperior temporal sulcus, similar to the area found in a previous work using only subjects with the same *GRN* mutation (Moreno et al., 2013) and thus, chronological age was interchangeable with EYO. Even if the localization of the significant clusters were not the same when EYO was used in the interaction analysis instead of age, we believe that both the dorsofrontal and the supramarginal/temporal gyrus areas are important in the disease, as they both appear at the uncorrected level. However, the fact that the magnitude of the effects is small the inclusion of a large number of covariates might hide some results when we corrected for multiple comparisons.

Variants in the *TMEM106B* gene have been hypothesized to be a genetic modulator of risk for *GRN* carriers. Previous works suggests that *TMEM106B* minor allele in homozygosis (C/C in rs1990622) is protective or might delay the onset in individuals with pathogenic *GRN* mutations. On this basis, we evaluate the influence of the *TMEM106B* genotype in our results. Despite the fact that we did not find differences between the different *TMEM106B* genotypes, we found a trend suggesting that C/C carriers might present a lower loss of CTh by age than the T/C and T/T carriers in the left superior frontal cortex. The absence of statistical differences in these analyses may be consequence of the small sample of subjects carrying the C/C genotype in our series. This would be in consonance with previous works with functional MRI that found decreased brain connectivity within the middle frontal gyrus and the left frontoparietal network in *GRN* carriers with the risk *TMEM106B* allele in front those with the protective allele (Premi et al., 2014).

The main strength of this study lies in the large sample of presymptomatic subjects carrying mutations in *GRN*. We also acknowledge some limitations. First, our age-related results are based on cross-sectional rather than longitudinal data. Although our analysis suggests a faster atrophy in presymptomatic carriers, further studies with longitudinal data are needed to corroborate this hypothesis. Another limitation is the fact that our study includes different *GRN* mutations which may present different ages at symptom onset, and EYO was used in some of the analysis to overcome this limitation. Finally, the *TMEM106B* haplotype was not available in all subjects. This fact, combined with the low frequency of the C/C haplotype in our series, limit the validity of statistical analysis performed to evaluate the influence of the *TMEM106B* gene in *GRN* carriers.

5. Conclusions

In conclusion, despite no differences in CTh were found at the whole-group comparison, the proposed linear model showed that presymtomatic *GRN* carriers present a significantly greater loss of CTh with age and proximity to expected disease onset. These findings suggest a faster process of neuronal loss in carriers, supporting that structural neuroimaging might be useful to monitor the effect of disease-modifying therapies even in presymptomatic phases of the disease.

Role of the funding source

The funding sources have no role in the design of this study, its execution, analyses, interpretation of the data, or the decision to submit results.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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