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Distinctive age-related temporal cortical thinning in asymptomatic granulin gene mutation carriers

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ABSTRACT

Studies in asymptomatic granulin gene (*GRN*) mutation carriers are essential to improve our understanding of the pattern and timing of early morphologic brain changes in frontotemporal lobar degeneration. The main objectives of this study were to assess the effect of age in cortical thickness changes (CTh) in preclinical *GRN* mutation carriers and to study the relationship of CTh with cognitive performance in *GRN* mutation carriers. We calculated CTh maps in 13 asymptomatic carriers of the c.709-1G>A *GRN* mutation and 13 age- and sex-matched healthy subjects. Asymptomatic *GRN* mutation carriers presented different patterns of age-related cortical thinning in the right superior temporal and middle temporal gyri and the banks of the superior temporal sulcus bilaterally when compared with controls. Cortical thickness was correlated with neuropsychological test scores: Trail Making Tests A and B, and the Boston Naming Test. Distinctive age-related cortical thinning in asymptomatic *GRN* mutation carriers in lateral temporal cortices suggests an early and disease-specific effect in these areas.

1. Introduction

Mutations in the granulin gene (*GRN*; MIM# 138945) were identified in 2006 as a causal mechanism underlying frontotemporal lobar degeneration (FTLD) (Baker et al., 2006; Cruts et al., 2006). More than 60 pathogenic point mutations and some deletions in the *GRN* gene have been identified (Alzheimer Disease and Frontotemporal Dementia Mutation Database; http://www.molgen.ua.ac.be/FTDMutations); these account for approximately 10% of FTLD cases and in some series are the most common cause of genetic dementia. Our group identified the c.709-1G>A (Ala237Trpfsx4) mutation in the *GRN* gene in a relatively large series of patients with FTLD from the Basque Country (López de Munain et al., 2008; Moreno et al., 2009). Several studies have demonstrated that patients with FTLD in association with *GRN* mutations show an asymmetric and widespread pattern of gray matter loss, predominantly affecting the frontal, posterior temporal, and inferior parietal cortices (Beck et al., 2008; Rohrer et al., 2010; Whitwell et al., 2007, 2009). Little is known, however, about brain morphology in asymptomatic *GRN* mutation carriers. In *GRN* mutation carriers the age of clinical onset varies widely, even within the same family, and is not currently possible to predict the exact age of disease onset in an asymptomatic individual. However, as the penetrance of the disease increases with age, in a group, age could be considered a proxy measure of time to disease onset.

Semiautomatic methods of magnetic resonance imaging (MRI) processing, such as the surface-based measurement of cortical thickness (CTh), permit the calculation of vertex-to-vertex CTh statistics across the entire cortical mantle (Fischl and Dale, 2000), and comparison of extensive cortical regions or atlas-based

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parcellations between groups more rapidly and with a higher interrater reliability (Desikan et al., 2006). CTh analysis has proven its usefulness in detecting widespread cortical abnormalities in early phases of several neurodegenerative diseases, even before clinical onset (Dickerson et al., 2009; Fortea et al., 2010).

The objectives of this study were: (1) to assess cortical structural changes in preclinical c.709-1G>A *GRN* mutation carriers and their correlation with age as an estimate of disease onset proximity; and (2) to study the relationship of CTh with cognitive performance in *GRN* mutation carriers.

2. Methods

2.1. Study population

Thirteen asymptomatic individuals carrying the c.709-1G>A *GRN* mutation (from 6 different families) and 13 control subjects were included in the study. As a control group (noncarriers) we included 9 first-degree relatives without the mutation and 4 control volunteers. We included these unrelated volunteers to prioritize age and sex matching that was not possible with only members of the FTLD-*GRN* families. Written informed consent was obtained from all subjects before enrollment and the study was approved by the Donostia Hospital Ethics Committee.

2.2. Clinical and cognitive assessment

Subjects were interviewed by an experienced clinician and no changes in cognitive function or behavior were detected. Further, they had no comorbidities known to affect brain structure. All the subjects belonging to the FTLD-*GRN* families (carriers and noncarriers) were administered an extensive battery of cognitive tests: the Mini-Mental State Examination, short form of the Wechsler Adult Intelligence Scale III, Continuous Performance Test, Digit Span, Trail Making Tests A and B (TMT-A and -B), Wisconsin Card Sorting Test, phonetic and semantic verbal fluency, Iowa Gambling Task, Boston Naming Test (BNT), verbal learning test from the Consortium to Establish a Registry for Alzheimer's Disease, and abbreviated Pictures of Facial Affect test. They all scored within the normal range in all the tests administered. In a previous study, with the same group of *GRN* mutation carriers and a slightly different control group (prioritizing being related rather than age and sex matching) we found that *GRN* mutation carriers obtained significantly lower scores than noncarrier relatives on the TMT-A, TMT-B, and BNT (Barandiaran et al., 2012).

2.3. Image acquisition

The MRI was performed on a 1.5 T scanner (Achieva Nova, Philips), with high-resolution volumetric turbo-field echo sequences (sagittal T1-weighted 3-D acquisition, repetition time [TR] = 7.2, echo time [TE] = 3.3, flip angle = 8°, matrix = 256 × 232, slice thickness of 1 mm, voxel dimensions of 1 × 1 × 1 mm, number of slices [NSA] = 1160). All the scans were acquired on the same MRI scanner and no hardware or software upgrades were carried out during the study period.

2.4. Processing of MRI images

We used the methods implemented in the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) to perform cortical surface reconstruction of the structural T1-weighted images. Briefly, the procedures carried out in the FreeSurfer pipeline include motion correction, skull stripping (Segonne et al., 2004), segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2002, 2004), tessellation of boundaries, and definition of the transition between tissue classes (Dale et al., 1999; Fischl and Dale, 2000). Then, CTh was calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex (Fischl and Dale, 2000). The automated FreeSurfer procedures also include parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006). The maps produced are not restricted to the voxel resolution of the original data, and hence are capable of detecting submillimeter differences between groups.

2.5. Statistical analysis

Group analyses of demographic and cognitive data were performed using Predictive Analysis Software (PASW version 17, IBM). Two-tailed Student *t* tests or analysis of variance were used for continuous and χ^2 tests for categorical variables. Correlation analysis was also performed between continuous variables.

As regards the imaging data, after visual inspection of cortical maps and subcortical segmentation, the reconstructed spherical maps were used to investigate patterns in the groups. Spherical vertex-wise data were registered to a standard template and smoothed using a full width at half maximum of 15 mm.

Analyses on whole-brain CTh maps were conducted using the Qdec tool from FreeSurfer. As a preliminary study we performed a *t* test comparison between groups. Age and sex were introduced as nuisance covariates in this comparison. Then, we examined the effect of age on the CTh maps separately for each group. For that purpose, whole brain CTh maps were regressed against the age of the subjects in 2 separate analyses for controls and mutation carriers. This separate analysis was performed to discriminate effects caused by the mutation from those provoked by age itself. Furthermore, a complementary analysis of the interference between age and group effects was performed with all the subjects. The interference analysis was designed to detect areas in which the slope of the age-CTh correlation differed between groups. Finally, we explored the correlations between whole-brain CTh and the cognitive tests previously found to be significantly different between *GRN* mutation carriers and noncarriers (TMT-A, TMT-B, and BNT scores) (Barandiaran et al., 2012).

In all the analyses, resulting maps were corrected for family-wise errors (FWEs) using Monte Carlo simulations with 10,000 iterations, and only clusters with a corrected cluster-wise threshold of $p < 0.05$ were considered. Lastly, the average CTh within the atlas-based parcellations (Desikan et al., 2006) was extracted and we examined correlations between age and these measures in each group using Pearson correlation implemented in PASW software. In addition, a multivariate analysis of age by group interaction effects was also modeled.

3. Results

Carriers had a mean age of 53.77 (SD, 11.50; range: 24–71 years) and noncarriers 52.77 (SD,13.78; range, 24–71) years. The male/female ratio was 6/7 in both groups. There were no significant differences in age or sex between the groups. Individual results for the neuropsychological tests in *GRN* mutation carriers are shown in Supplementary Table 1.

3.1. Cortical thickness group comparisons

There were no significant differences between carriers and controls in whole brain CTh maps after correcting for multiple comparisons.