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Association of Initial Side of Brain Atrophy With Clinical Features and Disease Progression in Patients With *GRN* Frontotemporal Dementia

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Abstract

Background and Objectives

Pathogenic variants in the *GRN* gene cause frontotemporal dementia (FTD-*GRN*) with marked brain asymmetry. This study aims to assess whether the disease progression of FTD-*GRN* depends on the initial side of the atrophy. We also investigated the potential use of brain asymmetry as a biomarker of the disease.

Methods

Retrospective examination of data from the prospective Genetic Frontotemporal Initiative (GENFI) cohort study that recruits individuals who carry or were at risk of carrying a pathogenic variant causing FTD. GENFI participants underwent a standardized clinical and neuropsychological assessment, MRI, and a blood sample test yearly. We generated an asymmetry index for brain MRI to characterize brain asymmetry in participants with or at risk of FTD-*GRN*. Depending on the side of the asymmetry, we classified symptomatic *GRN* patients as

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Coinvestigators are listed in the supplemental digital content available at Neurology.org/N.

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Glossary

bvFTD = behavioral variant FTD; **EYO** = estimated years to onset; **FPI** = Frontotemporal Prevention Initiative; **FTD** = frontotemporal dementia; **FTD-FRS** = Frontotemporal Dementia Rating Scale; **GENFI** = Genetic Frontotemporal Initiative; **MMSE** = Mini-Mental State Examination; **NfL** = neurofilament light chain; **NIHR** = National Institute for Health Research; **PPA** = primary progressive aphasia.

right-*GRN* or left-*GRN* and compared their clinical features and disease progression. We generated generalized additive models to study how the asymmetry index evolves in carriers and noncarriers and compare its models with others created with volumetric values and plasma neurofilament light chain.

Results

A total of 399 participants (mean age 49.7 years, 59% female) were included (63 symptomatic carriers, 177 presymptomatic carriers, and 159 noncarriers). Symptomatic carriers showed higher brain asymmetry (11.6) than noncarriers (1.0, $p < 0.001$) and presymptomatic carriers (1.0, $p < 0.001$), making it possible to classify most of them as right-*GRN* (n = 21) or left-*GRN* (n = 36). Patients with right-*GRN* showed more disease severity at baseline ($\beta = 6.9$, 95% CI 2.4–11.0, $p = 0.003$) but a lower deterioration by year ($\beta = -1.5$, 95% CI −2.7 to −0.31, $p = 0.015$) than patients with left-*GRN*. Brain asymmetry could be found in *GRN* carriers 10.4 years before the onset of the symptoms (standard difference 0.85, CI 0.01–1.68).

Discussion

FTD-*GRN* affects the brain hemispheres asymmetrically and causes 2 anatomical asymmetry patterns depending on the side of the disease onset. We demonstrated that these 2 anatomical asymmetry patterns present different symptoms, severity at the time of the first visit, and different disease courses. Our results also suggest brain asymmetry as a possible biomarker of conversion in *GRN* carriers.

Introduction

Heterozygous sequence variants in the progranulin (*GRN*) gene are one of the most common causes of familial frontotemporal dementia (FTD).[1,2] More than 100 *GRN* pathogenic variants are known, most of which cause disease due to progranulin haploinsufficiency.[3] The ensuing disease is a rapidly progressive FTD, but with a high heterogeneity of symptoms, including behavioral changes, language impairment, executive dysfunction, and parkinsonism.[4,5] This clinical heterogeneity leads to a presentation in different clinical syndromes, such as the behavioral variant FTD (bvFTD), primary progressive aphasia (PPA), corticobasal syndrome (CBS), and others.[6]

One of the hallmarks of FTD due to *GRN* pathogenic variants (FTD-*GRN*) is the asymmetric nature of brain atrophy in neuroimaging involving the frontal, temporal, and also parietal brain lobes.[7–9] The mechanism behind this asymmetry remains unclear but suggests a focal rather than diffuse onset, affecting one side before the other. The clinical syndrome largely depends on the side of this atrophy with most aphasic syndromes showing left (dominant hemisphere) atrophy. Despite these well-known clinical differences between patients with left (left-*GRN*) and right (right-*GRN*) atrophy, so far, no studies have analyzed the clinical and prognostic differences between right-*GRN* and left-*GRN* syndromes. At this moment, when clinical trials for modifying therapies for FTD-*GRN* are underway, understanding the actual natural course of the disease and its side variations is critical.[10] Many of these clinical trials incorporate outcomes such as the Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center for Frontotemporal Lobar Degeneration (CDR plus NACC FTLD) score, a semistructured global assessment score to stage the severity of dementia in FTD, which evaluates highly lateralized functions in the brain (such as language impairment). We hypothesize that the natural course of scores of these outcomes may differ between patients with right-*GRN* and left-*GRN*.[11]

Experience with other neurodegenerative diseases suggests that treating *GRN* carriers will be most successful if started early in the disease's course, even before symptoms appear. However, the age at onset in *GRN* carriers widely differs between individuals (even between those with the same pathogenic variant), emphasizing the crucial need for biomarkers to predict disease onset.[6] Plasma neurofilament light chain (NfL) and brain volumetry are the most promising onset biomarkers in FTD. A recent work from the Frontotemporal Prevention Initiative (FPI) concluded that, unlike in patients with *chromosome 9 open reading frame* and *microtubule-associated protein tau*, NfL elevations precede brain atrophy by several years in *GRN* carriers. Notwithstanding, this and other studies do not consider the asymmetric nature of atrophy in *GRN* carriers, which can lead to a loss of power in the detection of early brain changes.[12]

In this study, we asked whether the clinical presentation and disease progression of FTD-*GRN* depend on the initial side of the atrophy. With this aim, we classify patients with *GRN* from

the Genetic Frontotemporal Initiative (GENFI) as right-*GRN* or left-*GRN* and compare their clinical presentation and disease evolution. Finally, we also analyze the usefulness of brain asymmetry as a biomarker of the disease.

Methods

Participants

From January 2012 to January 2021, a total of 399 participants with FTD due to *GRN* pathogenic variants or at risk of it because of a first-degree relative carrying pathogenic variants were included from the data freeze 6 of the GENFI. The GENFI is a group of research centers across Europe and Canada with expertise in familial FTD. We recruited participants who were either known carriers of a pathogenic variant leading to FTD or at risk of carrying a pathogenic variant because a first-degree relative was a known symptomatic carrier.[13]

Participants in the GENFI cohort underwent a standardized clinical examination, a neuropsychological evaluation, a blood extraction, and brain MRI yearly. For each participant and visit, the estimated year to onset (EYO) was calculated considering the difference between the participants' age and the average familial age at symptom onset. Participants were classified as symptomatic if they met either prodromal criteria (onset of mild symptoms suggesting a disorder within the FTD spectrum but not fully meeting diagnostic criteria)[14] or fully symptomatic criteria (meeting diagnostic criteria for FTD).[15,16] Participants at risk (because of having a first-degree relative carrying a pathogenic variant) were classified as presymptomatic carriers or noncarriers depending on whether they carried the pathogenic variant. The disease stage of all participants was scored following the CDR plus NACC FTLD sum of boxes.[11] Global cognition was measured by the Mini-Mental State Examination (MMSE).[17] The revised version of the Cambridge Behavioural Inventory (CBI-R) and the FTD Rating Scale (FTD-FRS) were also implemented.[18,19] All participants were assessed with a comprehensive neuropsychological battery administered by trained neuropsychologists. The battery encompassed 3 cognitive domains. The language domain included the 30-item version of the Boston Naming Test[20] and a category fluency test.[21,22] The attention and executive functions domain consisted of the Trail Making Test A[23] and B[24] and a letter fluency test.[22] The Free and Cued Selective Reminding Test[25,26] was used to assess learning and encoding (free learning and total learning scores) and memory function (delayed free and total recall scores). Raw neuropsychological scores for each of these tests were converted to Z scores.

MRI Acquisition and Asymmetry Index Determination

The acquisition and processing procedures for neuroimaging have been described previously.[27] In brief, cortical volumes for the entire cortex and for the frontal, temporal, parietal, occipital, and insula cortices separately were generated using a multiatlas segmentation propagation approach following the brainCOLOR protocol. Volumes were corrected by the total intracranial volume.

For each brain MRI scan, we calculated an asymmetry index as follows[28–31]:

$$(\text{Left Volume} - \text{Right Volume})/((\text{Left Volume} + \text{Right Volume})/2) * 100$$

This index was calculated for the whole brain and each brain lobe, with values around 0 indicating brain symmetry, values under 0 indicating left atrophy, and values over 0 indicating right atrophy.

We implemented receiver operating characteristic (ROC) curves to determine the performance of the asymmetry index to distinguish between symptomatic carriers and noncarriers. The best cutoff point was selected following the Youden index.[32] Symptomatic patients over the positive value of this cutoff were classified as right-*GRN* while patients under the negative value of the cutoff were classified as left-*GRN*. Disease progression models of cognitive and neuropsychological variables for each group of patients (left-*GRN* and right-*GRN*) were created as described in the statistical methods section to establish the disease evolution in each of these groups.

Plasma NfL Measurement

Plasma NfL was measured using commercially available Single Molecule Array technology with an HD-1 analyzer (Simoa NF-Light Advantage Kit from Quanterix; Billerica, MA) according to the manufacturer's instructions. For some comparisons, the NfL variable was dichotomized in higher and lower NfL levels according to the cutoff proposed in previous works (19.8 pg/mL).[33]

Disease Progression Models for the Asymmetry Index

We generated disease progression models to study how the asymmetry index evolves in carriers and noncarriers. For these analyses, any type of asymmetry was considered, regardless of whether it was right or left, so the brain asymmetry index was converted to an absolute value. Models were created for the asymmetry of the whole brain and also for that of the frontal, temporal, parietal, and occipital lobes and the insula. Owing to the observed nonlinearity of the asymmetry index, these disease progression models were created using generalized additive models with the "mgcv" packages in R.[34] The asymmetry index was used as the response variable while EYO, sex, genetic status, and the interaction between EYO and genetic status were used as predictor variables.

To determine the performance of the asymmetry index for predicting the disease onset, we established the differences between carriers and noncarriers in those models and compared those differences with others obtained by models generated with the corresponding volumetric values and

plasma NfL as response variables. Comparisons between models were analyzed using standardized values of these variables with the "tidygam" R package.

Statistical Analyses

Statistical analyses were performed using R software V.4.0.3 (Vienna, Austria). Comparison of demographic and clinical data between groups was performed with the Wilcoxon rank-sum test for continuous variables and with the χ^2 test for categorical variables. For differences between participants with right-*GRN* and left-*GRN*, standardized effect measures were calculated with Cohen d. Correlations between variables were studied using the Pearson test. A linear mixed-effect model ("lmer" package) was generated to compare differences in the CDR plus NACC FTLD sum of boxes score between patients with left-*GRN* and right-*GRN*, with age and sex as covariates. Statistical significance was established in a 2-sided p value of <0.05. Corrections for multiple comparisons were performed using the Benjamini-Hochberg method when appropriate.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants. All procedures were approved by local ethics committees at each site.

Data Availability

Data can be obtained following the GENFI data-sharing agreement, subject to review by the GENFI data access committee, with final approval granted by the GENFI steering committee.

Results

Participants

Demographic and clinical data of the included participants are presented in Table 1. A total of 399 participants (63 symptomatic carriers, 177 presymptomatic carriers, and 159 noncarriers) were included. Symptomatic carriers were older than presymptomatic carriers and noncarriers ($p < 0.001$ for both). 8 presymptomatic carriers converted to symptomatic during the follow-up. The average number of visits per participant was 2.5, and the maximum follow-up duration was 8 years. A total of 1,091 MRI scans from these participants were analyzed. A subset of participants had available NfL levels (n = 291,607 observations). Figure 1 presents a flowchart of the study.

Brain Asymmetry by Clinical Status

Figure 2 shows the distribution of the asymmetry in each MRI scan for noncarriers, presymptomatic carriers, and symptomatic carriers. While noncarriers and presymptomatic carriers show a normal distribution with mean values around 0, the symptomatic group showed a wider distribution with most participants showing values far away from 0, with negative values indicating left atrophy and positive values indicating right atrophy. This distribution of the asymmetry values for the symptomatic carrier group was statistically different from those of the presymptomatic and control groups ($p < 0.001$ both). No statistical differences were found between the presymptomatic and control distributions of asymmetry. The ROC curve for the absolute asymmetric index to differentiate between symptomatic carriers and noncarriers showed an area under the curve (AUC) of 0.947 being the value of 3 the best cutoff value to differentiate symptomatic participants.

Demographics Differences Between Patients With Right-*GRN* and Left-*GRN*

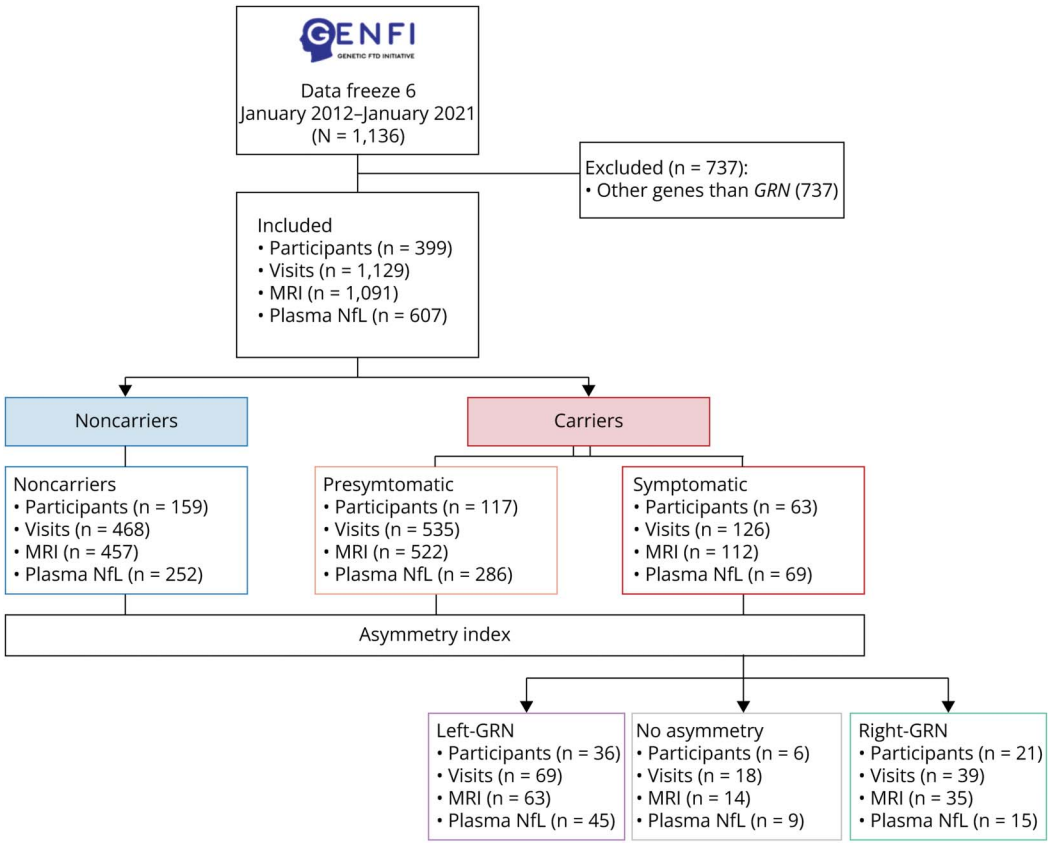
Considering this threshold, 36 symptomatic participants were classified as left-*GRN* and 21 as right-*GRN*. Table 2 presents the demographic and clinical characteristics of these 2 groups at baseline. No differences in sex, handedness, or age were found between the 2 groups. No particular *GRN* variant was associated with atrophy of the left or right side of the brain. There was a trend for more disease duration for right-*GRN* at baseline, but it was not statistically significant ($p = 0.11$). For the right-*GRN* group, the most common syndromic diagnosis was bvFTD, with apathy, loss of empathy, and hyperorality

Table 1 Demographics of Participants by Genetic Status

	Noncarriers (n = 159	Presymptomatic carriers (n = 177)	Symptomatic carriers (n = 63)	*p* Value
Sex, male (%)	67 (42)	65 (37)	30 (48)	—
Age, y, mean (SD)	48 (14)	46 (12)	64 (7)	<0.001[ab]
EYO, y, mean (SD)	−13 (15)	−14 (12)	3 (7)	<0.001[ab]
MMSE, mean (SD)	29.4 (1.0)	29.4 (1.0)	19.5 (7.4)	<0.001[ab]
Asymmetry index, mean (SD)	1.0 (0.8)	1.0 (0.7)	11.6 (6.6)	<0.001[ab]
Plasma NfL (pg/mL), mean (SD)	9 (5)	9 (8)	83 (47)	<0.001[ab]

Abbreviations: EYO = estimated year to onset. MMSE = Mini-Mental State Examination.
[a] Differences between noncarriers and symptomatic carriers.
[b] Differences between presymptomatic carriers and symptomatic carriers.

Figure 1 Flowchart Detailing the Participants, Visits, and Procedures of the Study



being the most affected domains. For patients with left-*GRN*, PPA was the most common diagnosis, especially because of fluency, grammar, and word retrieval impairment (eFigure 1).

CDR Plus NACC FTLD and Neuropsychological Evolution by Side

Patients with right-*GRN* and left-*GRN* present different disease evolutions (Figure 3A and eTable 1): At baseline, patients with right-*GRN* showed higher CDR plus NACC FTLD scores than patients with left-*GRN* (β = 6.9, 95% CI 2.4–11, p = 0.003). The same result was found when looking at the scores at the time of phenoconversion of those participants who converted during the follow-up (Figure 3B). Notwithstanding, participants with right-*GRN* showed a lower deterioration by year than participants with left-*GRN*, with both groups showing similar scores in the latest stages of the disease, suggesting a slower impairment of the CDR plus NACC FTLD score in these patients (β = −1.5, 95% CI −2.7 to −0.31, p = 0.015). Similar trends were found for each of the domains included in the CDR plus NACC FTLD, except for the language domain where the score was higher for the patients with left-*GRN* for the course of the entire disease (eFigure 2).

Patients with Left-*GRN* and right-*GRN* also showed different evolutions in their neuropsychological evaluations. Patients with left-*GRN* showed a higher decline in global cognitive performance on the MMSE and in most of the cognitive tests. On the contrary, patients with right-*GRN* showed worse impairment and a higher decline in behavioral inventory questionnaires such as the FTD-FRS or the CBI-R (eTable 2 and eFigures 3 and 4).

Brain Asymmetry by EYO

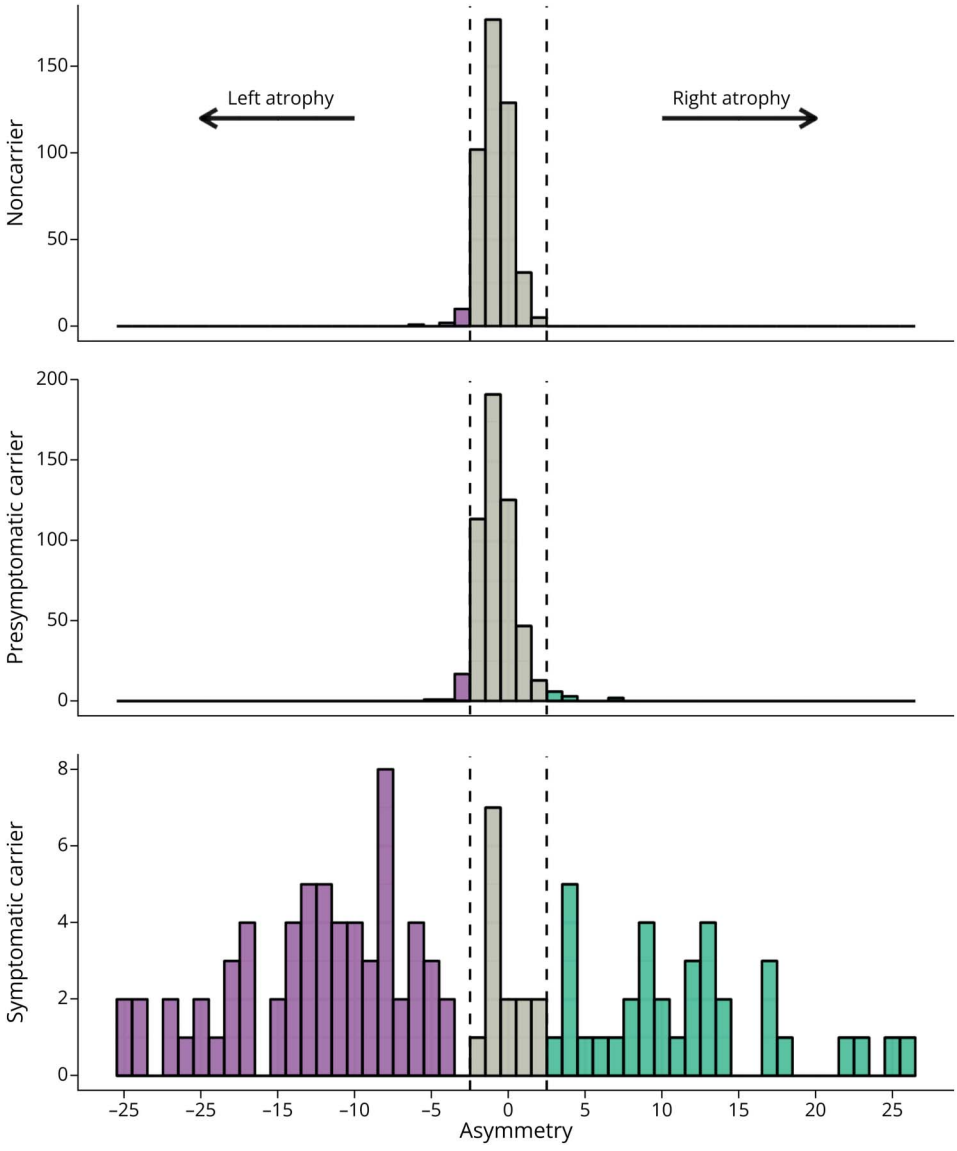
Figure 4A shows the distribution of the absolute asymmetry index by EYO for carriers and noncarriers. While noncarriers showed a plane line near the 0 value during all life, participants carrying *GRN* sequence pathogenic variants started to present brain asymmetry several years before the disease onset (−10.4 being the earliest EYO with statistical differences between carriers and noncarriers). Years after the symptom onset, the absolute asymmetry index tends to decrease, approaching 0 again.

To confirm that neuroimage asymmetry can be found before symptom onset, we also analyzed those carriers who converted from presymptomatic to symptomatic during the follow-up (Figure 4B and eFigure 5). In most of these converters, brain asymmetry could be found years before symptom onset.

Comparison Between Asymmetry Index and Plasma NfL

The asymmetry index showed a good correlation to plasma NfL (R = 0.73, p < 0.001, eFigure 6), with most symptomatic carriers showing values over the 2 proposed cutoff points.

Figure 2 Asymmetry Index Distribution by Genetic Status



Histograms showing the distribution of asymmetry in noncarriers (upper), presymptomatic carriers (middle), and symptomatic carriers (bottom). Values around 0 reflect no volumetric differences between hemispheres while positive values mean asymmetry due to right atrophy and negative values asymmetry due to left atrophy. The vertical dashed lines indicate the best cutoff values of asymmetry to differentiate symptomatic carriers from controls. Symptomatic carriers below the negative cutoff were classified as left-*GRN* while those above the positive cutoff were classified as right-*GRN*. Note that scales differ in the y-axis for the different subplots.

Within the presymptomatic carriers, those who presented NfL levels over the cutoff showed higher brain asymmetry than those who presented lower NfL levels ($p < 0.05$).

Model Comparisons for Predicting Onset

Finally, we compare the developed progression models for plasma NfL, brain volumetry, and the asymmetry index (Figure 5A and eFigure 7). We found differences between carriers and noncarriers at the earliest time point for plasma NfL and for the asymmetry index (10.4 years before expected onset) while differences in the whole brain volumetry were noted around 8 years before the expected onset.

When analyzing the asymmetry index in each brain lobe (Figure 5B and eFigure 8), we found the earliest differences between carriers and noncarriers in the parietal lobe (14 years before the expected onset), followed by the frontal and temporal lobes (10 years before the expected onset) and the insula (8 years before the expected onset). We did not find differences before the expected onset for the occipital lobe.

Discussion

Although brain asymmetry in patients with FTD-*GRN* has been previously well documented, its clinical consequences have been poorly assessed so far. In this work, we explore in depth the consequences of brain asymmetry in FTD-*GRN* and demonstrate that patients with right-*GRN* and left-*GRN* show important differences in their clinical phenotype and their clinical progression. In addition, our data demonstrate that the asymmetry between brain hemispheres might be an interesting biomarker to predict symptom onset.

Table 2 Patient Characteristics by Side

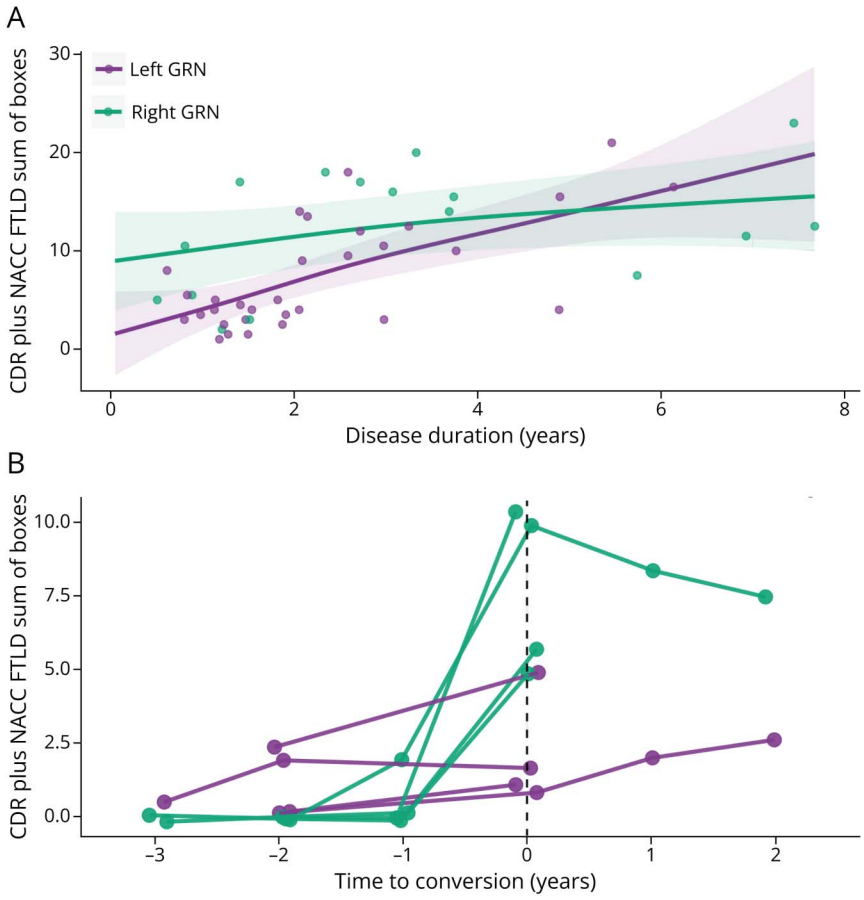
	Patients with left-*GRN* n = 36	Patients with right-*GRN* n = 21	*p* Value	Cohen d effect size
Sex, male, n (%)	15 (42)	11 (52)	0.4	NA
Left-handed, n (%)	1 (3.7)	1 (7.1)	>0.9	NA
Age, y, mean (SD)	63 (9)	64 (7)	0.7	0.07
Age at onset, y, mean, (SD)	61 (8)	61 (7)	>0.9	0.07
Duration, y, mean (SD)	2.46 (1.43)	3.50 (2.43)	0.11	0.52
EYO, mean (SD)	1 (8)	2 (7)	0.4	0.04
Asymmetry index, median (SD)	13 (5)	13 (7)	0.8	0.01
MMSE, mean (SD)	19 (8)	22 (7)	0.3	0.19
CDR plus NACC FTLD SOB median (IQR)	4.5 (7.5)	12.5 (9.5)	<0.01	0.90
Plasma NfL, mean (SD)	82 (47)	71(38)	0.7	0.32
Diagnosis at onset (%)				
bvFTD	8 (23)	16 (80)		
PPA	25 (71)	2 (10)		
CBS	1 (2.9)	0 (0)	<0.001	NA
Dementia-NOS	0 (0)	1 (5.0)		
Other	1 (2.9)	1 (5.0)		

Abbreviations: bvFTD = behavioral variant FTD; CBS = corticobasal syndrome; CDR plus NACC FTLD SOB = the Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center for Frontotemporal Lobar Degeneration sum of boxes; Dementia-NOS = dementia not otherwise specified; EYO = estimated years to onset; MMSE = Mini-Mental State Examination; PPA = primary progressive aphasia.

Several previous studies have reported considerable phenotypic variability in FTD-*GRN*.[4,6,7,35–37] Our work shows that this variability is partially explained by the 2 anatomical asymmetry patterns, in which most of the patients with right-*GRN* present with bvFTD and most of the patients with left-*GRN* with PPA. However, considerable phenotypic heterogeneity remains with other carriers presenting with other lateralized syndromes such as CBS or even not meeting clinical criteria because of atypical features. Our work also demonstrates differences in the clinical progression between these 2 anatomical asymmetry patterns, with the left-*GRN* phenotype presenting a faster disease progression while the right-*GRN* shows more severe disease at diagnosis. The faster progression in left-*GRN* could be attributed to 2 factors: the relevance of left-sided brain functions, such as the language, in many severity scores (such as the CDR plus NACC FTLD) or an inherent biological difference in the disease. The absence of significant differences in NfL levels between the 2 groups of patients supports the first option. Furthermore, because language is a particularly relevant brain function, its alteration might also influence the performance of other cognitive and functional outcomes that rely on unimpaired language. However, the clinical staging at baseline is lower for patients with left-*GRN*. We hypothesize that this is due to an earlier diagnosis when the disease starts in the left hemisphere because it contains more eloquent brain areas. Against this hypothesis, we do not find statistical differences in the age at onset and the duration of the disease between patients with left-*GRN* and right-*GRN*.

Because *GRN* variant carriers showed a wide variability in the age at onset of the disease, even between participants with the same pathogenic variant or from the same family, there is a crucial need for biomarkers indicating the onset of the disease.[6] Several studies have evaluated the usefulness of neuroimaging as a biomarker of conversion with divergent results[8,27,38–45]: some of these studies did not find differences between presymptomatic carriers and noncarriers while others found differences in years before the clinical onset, especially in the frontal, temporal, and parietal lobes and the insula. Recent work from the FPI pointed NfL as a more valuable conversion biomarker than brain atrophy in *GRN* carriers.[12,33] Nonetheless, these results might be a consequence of not taking into account the asymmetrical nature of the FTD-*GRN* disease: some of these studies consider both hemispheres together (including the less affected hemisphere, so making it more difficult to find differences between carriers and noncarriers) while others evaluated right and left hemispheres separately but without considering which of them is the most affected in each participant (so considering right and left *GRN* cases together). From our point of view, considering brain asymmetry is a better approach to assessing the very first brain changes in *GRN* carriers. Owing to brain asymmetry being uncommon in the general population, its appearance in the neuroimage might be

Figure 3 Disease Progression in Patients With Left-*GRN* and Right-*GRN*



Evolution of the CDR plus NACC FTLD sum of boxes scores by disease duration in left-*GRN* (purple) and right-*GRN* (green) in (A) all symptomatic patients and (B) presymptomatic carriers who converted to left-*GRN* or right-*GRN* syndromes during the follow-up. CDR plus NACC FTLD = the Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center for Frontotemporal Lobar Degeneration.

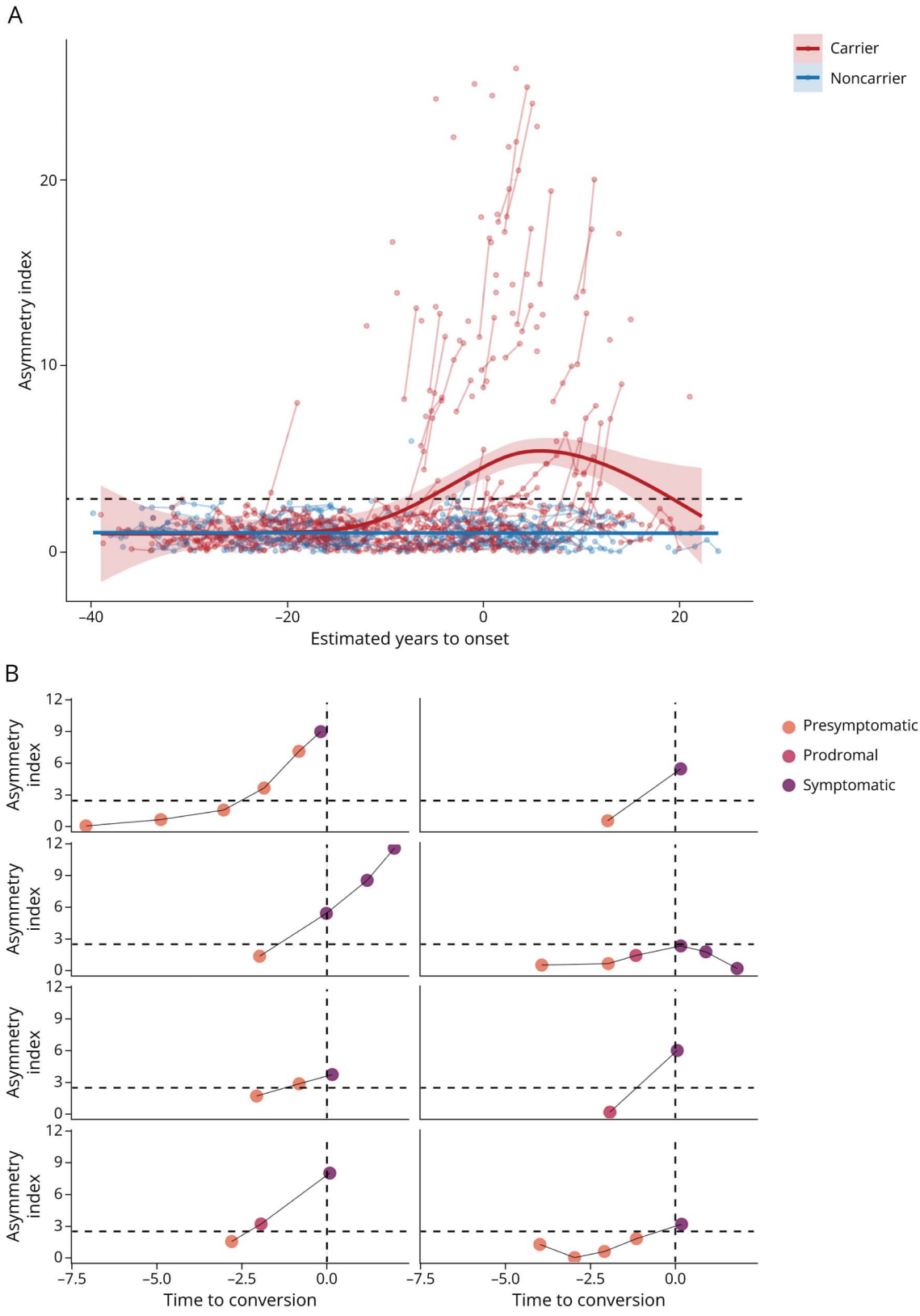
highly suggestive of the onset of the disease. In that line, our work demonstrates that brain asymmetry can be detected in *GRN* carriers years before the onset of the disease, earlier than volumetric changes, and with a very similar progression pattern to other proposed biomarkers such as NfL. Of note, parietal lobes were the earliest region found to be asymmetrical in our study. Previous studies have shown relevant atrophy in the parietal lobes, but our study points to this region as one of the first involved in the disease.[8,27,46,47]

Our work also shows that the brain asymmetry index follows a nonlinear trajectory (resembling an upside-down "*U*") during the FTD-*GRN* disease: the asymmetry index rises years before the expected onset, but with an inflection point around the sixth year of the disease, after which the asymmetry index decreases again to values around 0. We hypothesize 2 explanations for this finding. One possible explanation is that, after years of disease, the neurodegeneration of the latest affected hemisphere becomes more relevant, resulting in less asymmetry due to bilateral atrophy. Another possible explanation is the existence of 2 different populations of *GRN* carriers, one of them presenting protection to the disease and leading to observations without asymmetry years after the expected onset of the disease. The knowledge of genetic modifiers of the FTD-*GRN* disease as the TMEM106B might support this last hypothesis.[48,49] In the first case scenario, the nonlinearity of the asymmetry index may mean that this index is not a good biomarker of the progression of the disease.

Our findings may have important implications for the design of future clinical trials in patients with *GRN*. On the one hand, the finding of different course progressions in patients with right-*GRN* and left-*GRN* might support the need for patient stratification based on the affected hemisphere and notes the relevance of seeking outcomes less influenced by language function. On the other hand, the use of brain asymmetry as an onset biomarker could help to identify presymptomatic carriers close to conversion and to predict the initially affected side (information not provided by other biomarkers of conversion such as NfL).

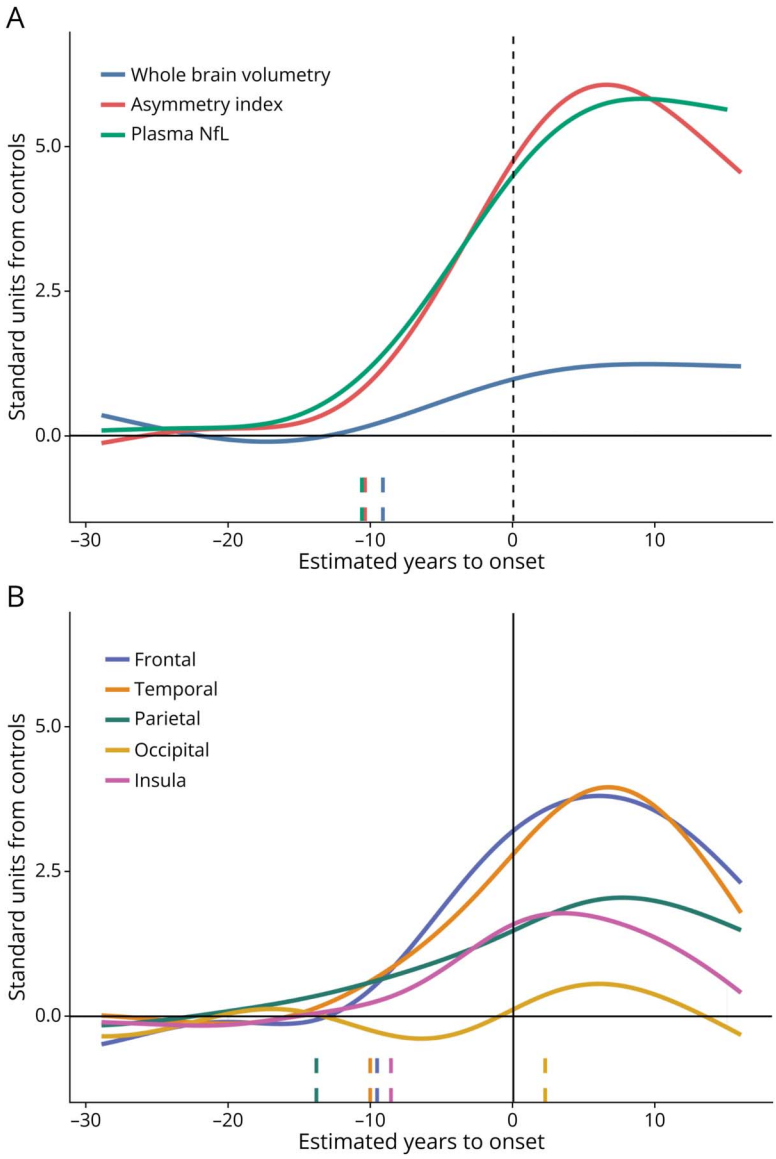
This study has some limitations: despite the multicenter effort of the GENFI cohort leading to a relatively large sample, the low prevalence of the FTD-*GRN* disease results in some subgroups with a small sample size, especially from individuals who converted during the follow-up. Our study may also suffer some selection bias: because the GENFI study includes only patients with known pathogenic variants, patients with an atypical phenotype may have been undiagnosed and, therefore,

Figure 4 Asymmetry Index Trajectories



(A) Trajectories of the absolute asymmetry index by the estimated years to onset in *GRN* pathogenic variant carriers (red) and noncarriers (blue). (B) Distribution of the asymmetry index in presymptomatic carriers who converted during the follow-up.

Figure 5 Models of the Asymmetry Index and Other Onset Biomarkers



Standardized difference between all pathogenic variant carriers and noncarriers in cortical gray matter volumetric imaging measures vs estimated years to expected symptom onset. Individual data points were not plotted to prevent the disclosure of genetic status. The time at which the upper 95% CI for each curve crosses 0 on the y-axis (the point at which a significant difference exists between pathogenic variant carriers and noncarriers) is shown on the x-axis. Individual curves with 95% CIs are presented in eFigures 5 and 6.

not represented in this work. In addition, the latest stages of the disease might be underrepresented because of the difficulty in performing MRI on participants in the last stages of the disease. In addition, as mentioned before, known genetic modifiers of the disease, such as TMEM106B, were not included in the study. One remaining question, not solved in this study, is the pathologic mechanism underlying the brain asymmetry in FTD-*GRN*. Until now, it has not been determined which pathogenic processes cause carriers of pathogenic *GRN* variants to exhibit predominant right or left neurodegeneration. Of note, brain asymmetry might also be found in other neurodegenerative diseases such as Alzheimer disease or sporadic FTD. Potential mechanisms include differential vulnerability of brain regions, variations in progranulin expression, asymmetric inflammatory responses, and differences in synaptic and network disruption. In addition, environmental or lifestyle factors may also contribute to the observed asymmetries. Further research is needed to elucidate these pathologic processes.

In summary, our work shows that *GRN* affects the brain hemispheres asymmetrically, leading to 2 well-differentiated syndromes that we call right-*GRN* or left-*GRN* depending on the predominance of brain atrophy. We demonstrated that these 2 anatomical asymmetry patterns present with different symptoms and different disease progression, a finding that could be considered in clinical trials. Finally, we also demonstrate that brain asymmetry is a good biomarker for predicting conversion in *GRN* carriers.

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Continued

Appendix 1 *(continued)*

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Continued

Appendix 1 *(continued)*

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Continued

Appendix 1 *(continued)*

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Coinvestigators are listed at Neurology.org/N.

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