Voxel-based morphometry patterns of atrophy in FTLD with mutations in *MAPT* or *PGRN*

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ABSTRACT

Objective: To compare patterns of gray matter loss in subjects with mutations in the progranulin (*PGRN*) gene to subjects with mutations in the microtubule-associated protein tau (*MAPT*) gene.

Methods: We identified all subjects seen at the Mayo Clinic, Rochester, MN, who had screened positive for mutations in *PGRN* or *MAPT* and had a head MRI. Twelve cases with mutations in the *PGRN* gene were matched by time from disease onset to scan to 12 subjects with mutations in the *MAPT* gene. Voxel-based morphometry was used to assess patterns of gray matter loss in the *PGRN* and *MAPT* groups compared to a control cohort, and compared to each other. *MAPT* subjects were younger than the *PGRN* subjects; therefore, each group was also compared to a specific age-matched control group.

Results: Both *PGRN* and *MAPT* groups showed gray matter loss in frontal, temporal, and parietal lobes compared to controls, although loss was predominantly identified in posterior temporal and parietal lobes in *PGRN* and anteromedial temporal lobes in *MAPT*. The *MAPT* group had greater loss compared to healthy subjects of the same age than the *PGRN* subjects when compared to healthy subjects of the same age. The *MAPT* subjects showed greater gray matter loss in the medial temporal lobes, insula, and putamen than the *PGRN* subjects.

Conclusion: These results increase understanding of the biology of these disorders and suggest that patterns of atrophy on MRI may be useful to aid in the differentiation of groups of *PGRN* and *MAPT* mutation carriers. ***Neurology*® 2009;72:813–820**

GLOSSARY

AD = Alzheimer disease; **ADPR** = Alzheimer's Disease Patient Registry; **ADRC** = Alzheimer's Disease Research Center; **bvFTD** = behavioral variant frontotemporal dementia; **bvFTD+P** = bvFTD with parkinsonism; **CBS** = corticobasal syndrome; **CDR-SB** = Clinical Dementia Rating scale sum of boxes; **DRS** = Dementia Rating Scale; **FTLD** = frontotemporal lobar degeneration; **MAPT** = microtubule-associated protein tau; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **PGRN** = progranulin; **PPA** = primary progressive aphasia; **STMS** = Short Test of Mental Status; **VBM** = voxel-based morphometry.

Frontotemporal lobar degeneration (FTLD) is a heterogenous progressive disorder that consists of a number of different clinical and pathologic variants. Approximately 40% of subjects have a family history with an autosomal dominant pattern of inheritance.[1,2] Two of the most commonly mutated genes are the microtubule-associated protein tau (*MAPT*) gene[3,4] and the progranulin (*PGRN*) gene[5,6] that are both located on chromosome 17q21. Mutations in these genes account in combination for approximately 10–20% of all FTLD subjects.[7,8] Mutations in *PGRN* are associated with deposition of TAR DNA-binding protein 43 (TDP-43)- and ubiquitin-positive neuronal inclusions

Table 1   Subject demographics

	Disease groups		Controls		
	PGRN (n = 12)	**MAPT** (n = 12)	**All controls** (n = 24)	**Old controls** (n = 12)	**Young controls** (n = 12)
No. of women (%)	6 (50)	7 (58)	13 (54)	6 (50)	7 (58)
Education, y	12 (12-16)	12 (9-18)	13 (12-20)	13 (12-16)	14 (12-20)
Age at scan, y	63 (52-84)*	49 (25-65)	55 (27-84)	63 (53-84)	49 (27-65)
Age at onset, y	58 (49-83)*	44 (24-63)	NA	NA	NA
Time from onset to scan, y	2.8 (0.6-7.1)	2.4 (0.5-6.5)	NA	NA	NA
Time from onset to death, y	7.0 (5-9.4)	6.3 (5-11)	NA	NA	NA
MMSE (/30)	22 (4-27)†‡	26 (10-30)†‡	30 (27-30)	30 (28-30)	30 (27-30)
STMS (/38)	28 (21-34)†‡	28 (11-36)†‡	36 (34-38)	36 (35-38)	36 (34-38)
DRS (/144)	102 (85-119)†‡	121 (76-139)†‡	140 (125-143)	140 (125-143)	141 (132-143)
CDR-SB (/18)	6 (0.5-18)†‡	4 (0.5-9)†‡	0 (0-0)	0 (0-0)	0 (0-0)

Data shown as median (range). Time from disease onset to death was available in nine *PGRN* and six *MAPT* cases.
*Significant differences between *PGRN* and *MAPT* subjects at $p < 0.001$.
†Significant differences between the disease groups and their matched control group at $p < 0.05$.
‡Significant differences between the disease groups and the entire control cohort at $p < 0.05$.
MMSE = Mini-Mental State Examination; STMS = Short Test of Mental Status; DRS = Dementia Rating Scale; CDR-SB = Clinical Dementia Rating scale sum of boxes.

in the frontotemporal cortices and hippocampus (FTLD-U).[9,10] In contrast, mutations in *MAPT* are associated with deposits of the hyperphosphorylated protein tau in the form of intraneuronal neurofibrillary tangles or Pick bodies in the frontal and temporal cortices of the brain.[11,12] While both *PGRN* and *MAPT* mutations are associated with a clinical diagnosis of frontotemporal dementia, there is some suggestion that the specific clinical phenotypes associated with these mutations differ.[8,13-15]

Using an unbiased voxel-level technique called voxel-based morphometry (VBM), we previously demonstrated patterns of frontal, temporal, and parietal gray matter loss in subjects with mutations in the *PGRN* gene, and demonstrated that these patterns are more severe and widespread than those observed in sporadic *PGRN*-negative FTLD-U cases.[16] At an individual level, patterns of atrophy in *PGRN* have also been shown to be highly asymmetric.[13,14,17,18] Voxel-based morphometry has also been applied to subjects with mutations in *MAPT*, particularly those with a IVS10 + 16C>T mutation, and has revealed gray matter loss predominantly in the temporal lobes.[19] Atrophy in *MAPT* carriers has been shown to be relatively symmetric.[13,14] These studies therefore suggest anatomic differences between *PGRN* and *MAPT* carriers.

The aim of this study was to use VBM to compare the patterns of gray matter loss in *MAPT* and *PGRN* mutation carriers.

METHODS **Subject selection.** We identified all subjects seen at Mayo Clinic, Rochester, MN, who had screened positive for mutations in either *PGRN* or *MAPT*, were symptomatic and had a volumetric MRI scan. Twelve subjects, representing six families, were identified who had screened positive for mutations in *PGRN*. Sequencing analyses showed that five different *PGRN* mutations were present in our cohort: c.154delA (p.Thr52HisfsX2), c.910_911insTG (p.Trp304LeufsX58), c.1395_1396insC (p.Cys466LeufsX46), c.1145delC (p.Thr382SerfsX30), and c.138 + 1G>A (IVS1 + 1G>A). The demographic features for these subjects are shown in table 1 and the detailed clinical features and diagnoses are shown in table 2. Clinical diagnoses were made according to consensus criteria for mild cognitive impairment,[20] Alzheimer disease (AD),[21] behavioral variant frontotemporal dementia (bvFTD),[22] primary progressive aphasia,[23] and corticobasal syndrome (CBS).[24] Eight of these subjects have come to postmortem and all were given a diagnosis of FTLD-U. Imaging results have previously been published from these eight subjects.[16]

A total of 19 subjects were identified who had screened positive for mutations in *MAPT*. The 12 subjects with mutations in *PGRN* were frequency matched using time from disease onset to scan to 12 of the subjects with mutations in *MAPT*. In all subjects the first scan after the time of onset was used. This matching was performed to ensure that subjects in both groups had the disease for the same length of time. The 12 selected subjects represented seven families with six different *MAPT* mutations: c.1842T>G (p.Asn279Lys), c.1907C>T (p.Pro301L), c.1919G>A (p.Ser305Asn), c.1920 + 3G>A (IVS10 + 3G>A), c.1920 + 16C>T (IVS10 + 16C>T), and c.2170G>A

Table 2 Clinical features and diagnoses of each *PGRN* and *MAPT* subject

Subject	Age at onset, y	Gender	Initial diagnosis rendered	Clinical signs and symptoms at the onset of illness	Established diagnosis after years of follow-up
PGRN					
1	69	M	MCI	Executive deficits and memory loss	AD
2	67	M	MCI	Memory loss	MCI
3	61	F	PPA	Language deficit	PPA
4	60	M	bvFTD	Personality change	bvFTD
5	52	F	bvFTD	Personality change, executive dysfunction, and memory loss	bvFTD
6	49	M	PD	Parkinsonism	CBS
7	56	M	bvFTD	Personality change	bvFTD+P
8	56	F	AD	Memory loss	bvFTD+P
9	56	F	bvFTD	Personality change, executive dysfunction, and memory loss	bvFTD+P
10	83	F	bvFTD	Personality change	bvFTD
11	55	F	bvFTD+P	Personality change, executive dysfunction, and parkinsonian features	bvFTD+P
12	62	M	PPA	Language deficits	PPA
MAPT					
13	50	F	bvFTD	Personality change	bvFTD
14	42	M	bvFTD	Memory loss and personality change	bvFTD
15	43	M	MCI	Memory loss and language deficits	bvFTD
16	63	F	MCI	Memory loss	bvFTD
17	45	M	bvFTD+P	Language deficits, dizziness, and parkinsonian features	bvFTD+P
18	51	F	AD	Memory loss and executive dysfunction	bvFTD
19	31	F	bvFTD+P	Personality change and parkinsonian features	bvFTD+P
20	24	M	PPA	Language deficits	bvFTD
21	48	F	bvFTD+P	Personality changes and parkinsonian features	bvFTD+P*
22	36	F	bvFTD+P	Personality changes and parkinsonian features	bvFTD+P
23	48	M	PPA	Language deficits	PPA
24	39	F	bvFTD+P	Memory loss and parkinsonian features	bvFTD+P*

*These subjects are in a pallidopontonigral degeneration family.
MCI = mild cognitive impairment; AD = Alzheimer disease; PPA = primary progressive aphasia; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; bvFTD+P = bvFTD with parkinsonism.

(p.Gly389Arg). Subject demographics are shown in table 1 with clinical features and diagnoses shown in table 2. Four of these subjects underwent autopsy with pathologic findings of widespread tau deposition in neurons and glia.

The majority of all these cases had been prospectively studied in our Alzheimer's Disease Research Center (ADRC) or Alzheimer's Disease Patient Registry (ADPR). The historical records of all cases were reviewed by an expert in neurodegenerative diseases (K.A.J.) for the abstraction of data, including gender, age at onset, illness duration, Mini-Mental State Examination (MMSE),[25] Short Test of Mental Status (STMS),[26] Dementia Rating Scale (DRS),[27] and the Clinical Dementia Rating sum of boxes score (CDR-SB)[28] (table 1). Informed consent was obtained for participation in the studies, which were approved by the Mayo Institutional Review Board.

Each of the 24 subjects was then also matched by age and gender to a cognitively normal control subject. All control subjects were prospectively recruited into the ADRC or the ADPR

and were identified from the ADRC/ADPR database. Control subjects were cognitively normal individuals that had been seen in internal medicine for routine physical examinations and asked to enroll in the ADRC or ADPR. All subjects were then evaluated by a neurologist to verify the normal diagnosis. Controls were identified as individuals who 1) were independently functioning community dwellers, 2) did not have active neurologic or psychiatric conditions, 3) had no cognitive complaints, 4) had a normal neurologic and neurocognitive examination, and 5) were not taking any psychoactive medications in doses that would affect cognition.

Genetic analysis. Exons 0–13 and the 3′ untranslated region of the *PGRN* gene were amplified by PCR using our previously published primers and protocol.[5,7] Analysis of *MAPT* exons 1, 7, and 9–13 was also performed using primers and conditions that were previously described.[3] For both genes, the PCR amplicons were purified using the Multiscreen system (Millipore, Billerica,

MA) and then sequenced in both directions using Big Dye chemistry following manufacturer's protocol (Applied Biosystems, Foster City, CA). Sequence products were purified using the Montage system (Millipore) before being run on an ABI 3730 DNA Analyzer. Sequence data were analyzed using either SeqScape or Sequenom software.

Voxel-based morphometry. A standardized imaging protocol was performed on all subjects that included a coronal T1-weighted three-dimensional volumetric sequence with 124 contiguous partitions and 1.6 mm slice thickness (22×16.5 cm field of view, 25° flip angle). Patterns of cerebral atrophy were assessed using the automated and unbiased technique of VBM.[29] An optimized method of VBM was applied using both customized templates and prior probability maps,[30] implemented using SPM2 (http://www.fil.ion.ucl.ac.uk/spm). The processing steps were performed as previously described.[16] Briefly, all images were normalized to a customized template created from all subjects in the study. The spatial normalization was optimized by normalizing the gray matter images to the customized gray matter template. Images were segmented using customized prior probability maps, modulated, and smoothed with an 8 mm full-width at half-maximum smoothing kernel.

Three types of VBM comparisons were performed. First, statistical comparisons were performed between the *MAPT* mutation carriers and the entire control group and between *PGRN* mutation carriers and the entire control group. Adjustment for the potential confounders of age and gender was performed by including them as nuisance variables in the statistical model. This analysis was also repeated assessing only the *PGRN* and *MAPT* subjects with a clinical diagnosis of bvFTD (n = 7 *PGRN* and n = 11 *MAPT*) in order to account for potential clinical confounders. However, since the *MAPT* subjects were, as a group, approximately 14 years younger than the *PGRN* mutation carriers, we also divided the control population into two groups: 1) those subjects who were individually age-matched to the *MAPT* subjects (i.e., young control group), and 2) those subjects who were individually age-matched to the *PGRN* subjects (i.e., old control group). We therefore performed a second type of statistical comparison between the *PGRN* group and the old controls, and also the *MAPT* group and the young controls. Once again age and gender were included in the statistical models as nuisance variables. This analysis was important to determine how much of the atrophy in the *PGRN* group was due to age rather than the disease itself. The characteristics of the *PGRN* and *MAPT* mutation carriers and the control cohorts are shown in table 1. These results were assessed after correction for multiple comparisons using the false discovery rate at $p < 0.01$. Finally, direct comparisons were also performed between the *MAPT* carriers and the *PGRN* carriers, including age and gender as nuisance variables. The results of this analysis were assessed at a more lenient statistical threshold of $p < 0.001$ uncorrected for multiple comparisons due to the hypothesis-driven nature of this comparison.

Statistics. Statistical analyses were performed utilizing JMP computer software (JMP Software, version 6.0.0; SAS Institute Inc., Cary, NC) with α set at 0.05. Gender ratios were compared across groups with χ^2 test. Kruskal-Wallis test was used to compare continuous data across the three groups.

RESULTS The subject demographics are shown in table 1. The subjects with a mutation in *MAPT* were significantly younger at disease onset and scan than the subjects with a mutation in *PGRN*, although there was no difference between the groups in time

from disease onset to scan, disease duration (time from onset to death), gender ratio, or education. The cognitive test scores were significantly different between the disease groups and the control groups, but there were no significant differences between the *PGRN* and *MAPT* groups.

Figure 1 and table e-1 (on the *Neurology*® Web site at www.neurology.org) show the patterns of gray matter loss in the *PGRN* and *MAPT* groups when compared to the entire control cohort. Both disease groups showed widespread patterns of gray matter loss involving frontal, temporal, and parietal lobes, compared to controls. However, the distribution of gray matter loss differed across the two disease groups. In the *PGRN* group, gray matter loss was identified predominantly in posterior temporal regions, with severe involvement of parietal lobes and additional involvement of the posterior cingulate gyrus and precuneus. In the *MAPT* group, the gray matter loss was focused predominantly in the temporal lobes, particularly anterior and medial temporal lobes, with less involvement of the parietal lobes and no involvement of cingulate gyrus or precuneus. The cerebellum was also involved in the *MAPT* group. Very similar patterns of gray matter loss were observed in both the *PGRN* and *MAPT* groups when only subjects with bvFTD were assessed (figure e-1).
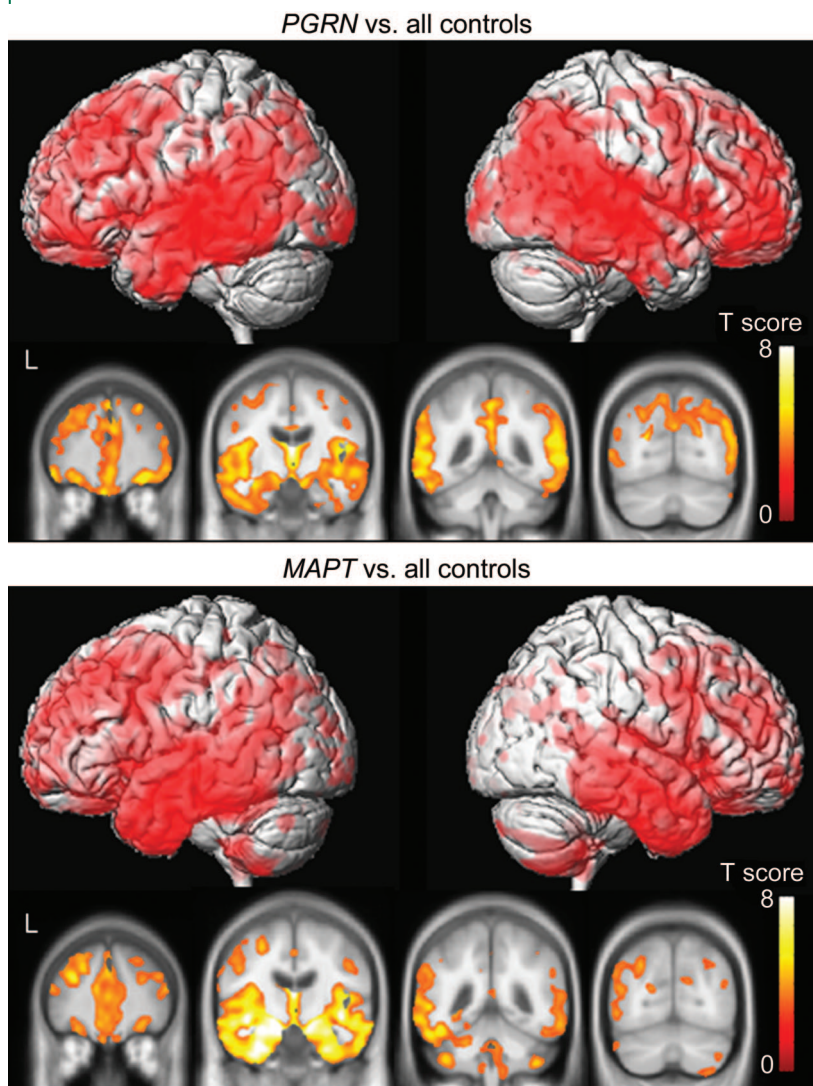
Figure 2 shows the patterns of gray matter loss in the *PGRN* and *MAPT* groups when each is compared to a specific age-matched control group. It is notable from this figure that the *PGRN* group shows a less severe and widespread pattern of gray matter loss compared to the age-matched old controls than the *MAPT* group compared to the age-matched young controls. The *PGRN* group shows gray matter loss mainly restricted to the posterior temporal lobe and parietal lobe compared to the old controls. The patterns of loss observed in the *MAPT* group compared to the young controls are similar to those identified in figure 1, with widespread involvement of the frontal, temporal, and parietal lobes, with particular focus on the anterior and medial temporal lobes, and some involvement of the cerebellum.

Direct comparisons were performed between the two groups. The subjects with mutations in *MAPT* showed greater gray matter loss predominantly in the temporal lobes than the subjects with mutations in *PGRN* (figure 3). Regions of loss were identified in the bilateral amygdala, hippocampus and parahippocampal gyrus, and left inferior temporal lobe, as well as the insula and left putamen. The reverse comparison showed that no regions of greater gray matter loss were identified in subjects with mutations in *PGRN* compared to subjects with mutations in *MAPT*.

Example MRI scans from individual cases with mutations in *PGRN* or *MAPT* illustrating these ob-

Figure 1 Patterns of gray matter loss in subjects with mutations in *PGRN* and subjects with mutations in *MAPT* compared to the entire control cohort

PGRN vs. all controls

MAPT vs. all controls

Results are shown on three-dimensional renders of the brain and coronal slices through the frontal, temporal, and parietal lobes.

neus was also present in the subjects with *PGRN* mutations compared to controls, suggesting that *PGRN* is associated with both medial and lateral parietal lobe damage. We have previously shown that subjects with *PGRN* mutations show a greater degree of parietal lobe involvement than subjects with FTLD-U without a mutation in *PGRN*.[16] The current study, however, shows that the parietal lobe is also affected in subjects with mutations in the *MAPT* gene and we found no differences in the parietal lobe between the *PGRN* and *MAPT* subjects on direct comparison. The involvement of the parietal lobe in *PGRN* concurs with the fact that subjects with *PGRN* can have a clinical presentation and diagnosis of AD or CBS.[8,13,17,18] However, our results show that the parietal gray matter loss is not driven solely by the presence of AD and CBS phenotypes since similar patterns of loss were observed in the bvFTD subjects with mutations in *PGRN*. Although the parietal lobe was affected in subjects with mutations in *MAPT* it was involved to a lesser degree than the frontal and temporal lobes, and therefore appears to be a feature of widespread disease rather than being the focus of loss as seen in *PGRN*.

A widespread pattern of frontotemporal gray matter loss was observed in the subjects with mutations in the *MAPT* gene, although, in contrast to the *PGRN* subjects, the most severe regions of loss were identified in the anteromedial temporal lobes. In fact, subjects with mutations in *MAPT* showed greater temporal lobe atrophy, particularly involving the medial temporal lobe, than the subjects with mutations in *PGRN* on direct comparison. Patterns of severe temporal lobe atrophy have previously been demonstrated in studies that have investigated subjects with tau exon mutations IVS10 + 16C>T,[19,33] IVS10 + 3G>A,[34] and p.Asn279Lys,[35,36] suggesting that *MAPT* mutations may predispose to temporal lobe atrophy. These findings fit with previous studies that have shown that while the majority of *MAPT* cases have a diagnosis of behavioral variant FTD,[8,13,15,37] a high proportion show language deficits.[8,15,17] Greater gray matter loss in *MAPT* subjects was also identified in the putamen. Reduced uptake of fluoro-L-dopa has previously been reported using PET in the striatum of subjects with pallidopontonigral degeneration and p.Asn279Lys mutations.[38] While in the comparisons with controls the *MAPT* group appeared to show greater involvement of the cerebellum than the *PGRN* group, this finding did not appear on direct comparison, suggesting that it is unlikely to be an important disease-specific finding.

The *MAPT* subjects were however approximately 14 years younger at disease onset and scan than the subjects with *PGRN* mutations. This trend for

served differences in patterns of atrophy are shown in figure e-2.

DISCUSSION In this study, we compared regional patterns of gray matter loss across subjects with mutations in *MAPT* and *PGRN* using automated and unbiased methodology. The subjects with mutations in the *PGRN* gene showed patterns of gray matter loss predominantly affecting the posterior temporal and parietal lobes, with additional involvement of the frontal lobes. Patterns of posterior temporal gray matter loss have previously been reported in subjects with a pathologic diagnosis of FTLD-U.[19,31] Atrophy of the parietal lobes[13,16-18,32] and parietal lobe dysfunction[32] have also been reported to be common in subjects with mutations in *PGRN*. Furthermore, parietal lobe atrophy was shown in a pathologic study.[9] Gray matter loss of the posterior cingulate and precu-

Figure 2 Patterns of gray matter loss in subjects with mutations in *PGRN* compared to age-matched old controls, and subjects with mutations in *MAPT* compared to age-matched young controls

PGRN vs. "old" controls
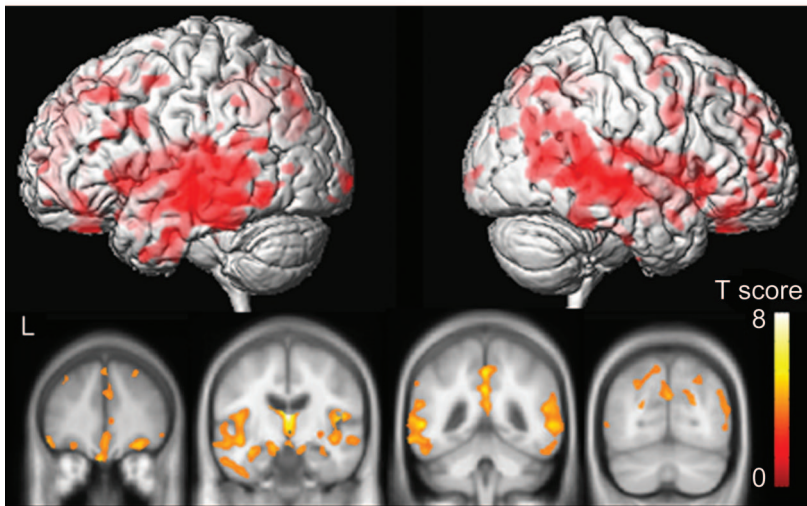
MAPT vs. "young" controls
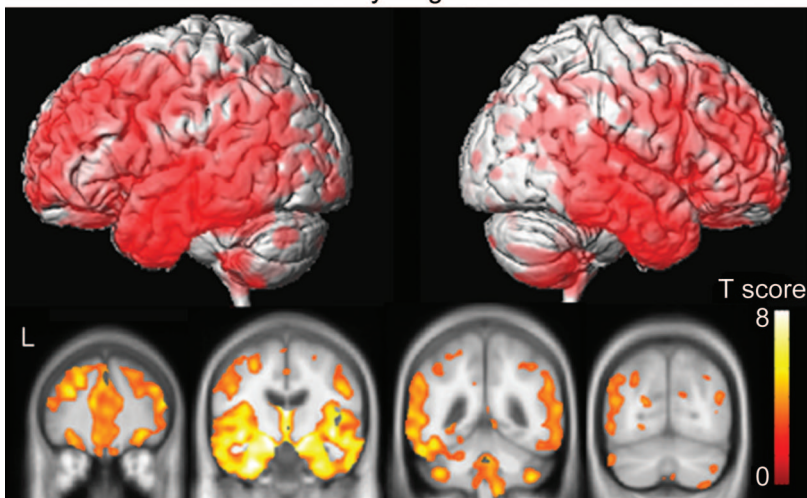
Results are shown on three-dimensional renders of the brain and coronal slices through the frontal, temporal, and parietal lobes.

able; however, in order to more accurately correct for this age difference, we compared the disease groups to different and specifically age-matched control subjects. This analysis showed that the *MAPT* subjects have greater gray matter loss compared to healthy subjects of the same age than the amount present in the *PGRN* subjects when compared to healthy subjects of the same age. The time from onset to scan was similar in the *PGRN* and *MAPT* groups and therefore one could infer from these cross-sectional results that the rate of gray matter atrophy may be higher in the *MAPT* subjects, since they have lost a greater degree of gray matter from normal in the same time. A trend for more severe atrophy in young-onset subjects has previously been demonstrated in subjects with AD.[39] These results suggest the same may be true for subjects with frontotemporal dementia. However, it has also been suggested that subjects with mutations in MAPT have a strong neurodevelopmental component with lower baseline functioning,[40] perhaps indicating that they also have a lower premorbid brain reserve. Longitudinal studies will be needed to solve this issue. The fact that less gray matter loss was observed when the *PGRN* group was compared to the old controls than when they were compared to the on average younger entire control cohort also suggests that significant age-related gray matter loss was present in the *PGRN* results shown in figure 1. In fact, the most striking difference in the *PGRN* maps between figure 1 and figure 2 was the lack of frontal lobe signal when *PGRN* subjects are compared with age-matched controls, suggesting that greatest gray matter loss in the old controls occurred in the frontal lobes.

The assessment of patterns and severity of gray matter loss could however be limited by the fact that subjects with mutations in *PGRN* typically show very asymmetric patterns of atrophy, affecting either the left or right hemisphere.[13,14,17,18] In contrast, subjects with *MAPT* mutations typically show more symmetric patterns of atrophy.[13,14] The asymmetry present in

younger age at onset in subjects with mutations in *MAPT* has been previously noted.[8,13] Age was included in the main analysis as a confounding vari-

Figure 3 Regions that show greater gray matter loss in subjects with mutations in *MAPT* compared to subjects with mutations in *PGRN*
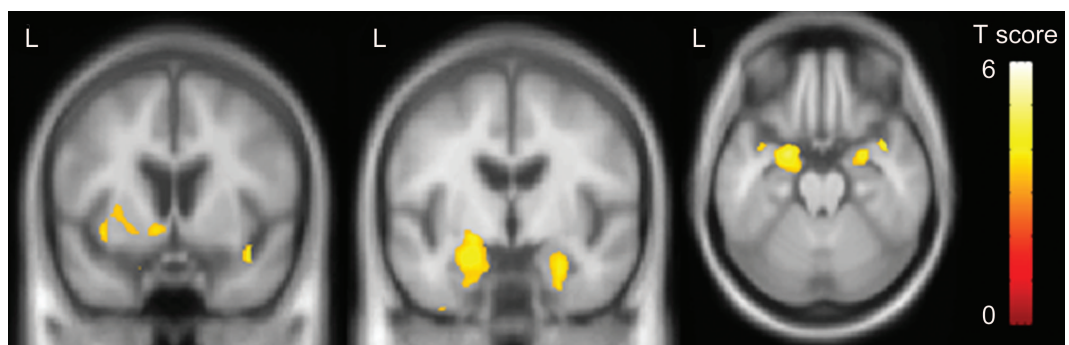
the *PGRN* subjects would not necessarily be evident from a VBM analysis, which averages the patterns of loss across groups of subjects. Variability in hemispheric atrophy could reduce the signal identified by the VBM analysis. The patterns of loss in each hemisphere are also more likely to be driven by fewer subjects in the *PGRN* group. Therefore, it will be important for these patterns of hemispheric atrophy to be confirmed in larger cohorts of subjects with mutations in *PGRN*.

While this is a group study and individual patterns of atrophy, and hence clinical phenotypes, may vary across these genetic types,[17] these results show trends for differences in patterns of atrophy on MRI across *PGRN* and *MAPT* mutation carriers. Both groups show involvement of the frontal, temporal, and parietal lobes, but there was a trend for subjects with mutations in *MAPT* to show a predominance of anteromedial temporal lobe atrophy while subjects with mutations in *PGRN* show heavy involvement of the posterior temporal and parietal lobes. These imaging findings, in conjunction with clinical measures, may aid in the differentiation of *PGRN* and *MAPT* mutation carriers. It will be important to determine whether these patterns can be identified early in the disease course, especially in asymptomatic family members, and therefore allow the early prediction of genetic status and hence resultant pathologic outcome.

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