Voxel-Based Morphometry in Frontotemporal Lobar Degeneration With Ubiquitin-Positive Inclusions With and Without Progranulin Mutations

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Background: Mutations in the progranulin gene (PGRN) have recently been identified as a cause of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) in some families.

Objective: To determine whether there is a difference in the patterns of atrophy in FTLD-U cases with and without PGRN mutations.

Design: Case-control study.

Setting: Brain bank of a tertiary care medical center.

Patients: Eight subjects who had screened positive for PGRN mutations (PGRN-positive) and who underwent volumetric magnetic resonance imaging were identified. Subjects were then matched by clinical diagnosis to a group of 8 subjects with a pathological diagnosis of FTLD-U who had screened negative for PGRN mutations (PGRN-negative). All subjects were then age-matched and sex-matched to a control subject.

Main Outcome Measures: Voxel-based morphometry was used to assess the patterns of gray matter atrophy in the PGRN-positive group compared with the PGRN-negative group and compared with controls.

Results: The PGRN-positive group showed a widespread and severe pattern of gray matter loss predominantly affecting the frontal, temporal, and parietal lobes. The PGRN-negative group showed a less severe pattern of gray matter loss restricted mainly to the temporal and frontal lobes. On direct comparison, the PGRN-positive group showed greater gray matter loss in the frontal and parietal lobes compared with the PGRN-negative group.

Conclusion: Findings from this study suggest that PGRN mutations may be associated with a specific and severe pattern of cerebral atrophy in subjects with FTLD-U.

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HERE ARE 3 WELL-RECOGNIZED CLINICAL VARIANTS OF FRONTOTEMPORAL LOBAR DEMENTIA (bvFTD), PROGRESSIVE NONFLUENT APHASIA, AND SEMANTIC DEMENTIA.1 THE bvFTD IS CHARACTERIZED BY BEHAVIORAL AND PERSONALITY CHANGES AND EXECUTIVE DYSFUNCTION, WHEREAS THE OTHER 2 VARIANTS ARE APHASIC SYNDROMES. FRONTOTEMPORAL LOBAR DEGENERATION CAN BE PATHOLOGICALLY CATEGORIZED INTO THOSE WITH TAU-POSITIVE INCLUSIONS AND THOSE WITH UBIQUITIN-POSITIVE INCLUSIONS.2 TWO RECENT STUDIES3,4 DEMONSTRATED THAT MUTATIONS IN THE PROGRANULIN GENE (PGRN) ARE ASSOCIATED WITH FRONTOTEMPORAL LOBAR DEGENERATION WITH UBIQUITIN-POSITIVE INCLUSIONS (FTLD-U).

The objective of this study was to determine whether subjects with FTLD-U and PGRN mutations have a signature pattern of gray matter atrophy. We hypothesized that the pattern of atrophy in FTLD-U cases with PGRN mutations would be no different from the pattern of atrophy in those without PGRN mutations.

METHODS

SUBJECTS

We identified 6 cases with a pathological diagnosis of FTLD-U from our autopsy database at the Mayo Clinic in Rochester that had frozen brain tissue or stored DNA blood that had screened positive for PGRN mutations (PGRN-positive) and that had usable volumetric head magnetic resonance (MR) images. Two additional cases without pathological confirmation were included; each had screened positive for PGRN mutations and had pathological confirmation in multiple siblings. All cases had been prospectively studied in the Alzheimer Disease Research Center or Alzheimer Disease Patient Registry at the Mayo Clinic in Rochester. The historical records of...
all cases were reviewed by 1 of us (K.A.J.) for the abstraction of data, including sex, age at disease onset, illness duration, Short Test of Mental Status score, and symptoms recorded by the treating physician up to the time of MR imaging (Table 1). We also abstracted information on whether parkinsonism, language impairment, or behavioral features developed before death. Parkinsonism was defined as the presence of 2 or more symptoms of tremor, bradykinesia, rigidity, or postural instability; language impairment was defined as word-finding difficulties, anomia, aphasia, or any loss of syntax, fluency, or comprehension; and behavioral features were defined as any change in the subject’s behavior or personality. Each PGRN-positive subject was then matched by clinical diagnosis to a subject who had screened negative for PGRN mutations (PGRN-negative). Six PGRN-positive subjects were diagnosed as having bvFTD and were matched to PGRN-negative subjects having a clinical diagnosis of bvFTD. One PGRN-positive subject had semantic dementia and was matched to a PGRN-negative subject with semantic dementia, and 1 PGRN-positive subject had left-sided corticobasal syndrome (CBS) and was matched to a PGRN-negative subject with left-sided CBS. This matching was important because the various clinical phenotypes of FTLD-U may have different patterns of gray matter atrophy. The objective of this study was to assess the effects of the PGRN mutation independent of clinical phenotype. Each PGRN-positive and PGRN-negative subject was age matched and sex matched to a healthy control subject.

### Table 1. Clinical Features of PGRN-Positive and PGRN-Negative Subjects

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age at Disease Onset, y</th>
<th>Illness Duration, y</th>
<th>STMS Score at the Time of MR Imaging</th>
<th>Diagnosis at the Time of MR Imaging*</th>
<th>Recorded Symptoms up to the Time of MR Imaging</th>
<th>Symptoms Present During the Entire Disease Course</th>
<th>Parkinsonism</th>
<th>Language Impairment</th>
<th>Behavioral Features</th>
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<tr>
<td><strong>PGRN-Negative Group</strong></td>
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<td></td>
</tr>
<tr>
<td>1/F/64</td>
<td>13</td>
<td>25</td>
<td>bvFTD</td>
<td>Personality change, apathy, loss of interest</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>2/F/62</td>
<td>8</td>
<td>34</td>
<td>bvFTD</td>
<td>Anhedonic, lack of initiative, poor judgment</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>3/M/45</td>
<td>13</td>
<td>26</td>
<td>bvFTD</td>
<td>Personality change, withdrawn, loss of initiative</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4/F/68</td>
<td>3</td>
<td>NA</td>
<td>CBS</td>
<td>Parkinsonism, L&gt;R limb apraxia</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5/F/64</td>
<td>6</td>
<td>34</td>
<td>bvFTD</td>
<td>Changes in behavior and personality</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>6/M/51</td>
<td>1</td>
<td>30</td>
<td>bvFTD</td>
<td>Executive dysfunction, decreased personal hygiene, inappropriate laughter, compulsive behaviors</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>7/F/59</td>
<td>7</td>
<td>26</td>
<td>Semantic dementia</td>
<td>Difficulty with naming of people and objects, circumlocutions, behavioral changes</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8/F/77</td>
<td>6</td>
<td>31</td>
<td>bvFTD</td>
<td>Personality change, executive dysfunction, paranoia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td><strong>PGRN-Positive Group</strong></td>
<td></td>
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<tr>
<td>9/M/69</td>
<td>7</td>
<td>28</td>
<td>bvFTD</td>
<td>Executive dysfunction, loss of attention, memory loss</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10/M/60</td>
<td>8</td>
<td>31</td>
<td>bvFTD</td>
<td>Personality change, executive dysfunction, memory loss</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11/F/52</td>
<td>5</td>
<td>23</td>
<td>bvFTD</td>
<td>Personality change, executive dysfunction, abulia, memory loss, decreased word output and fluency</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12/M/49</td>
<td>6</td>
<td>27</td>
<td>CBS</td>
<td>Parkinsonism, L&gt;R limb apraxia</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>13/M/56</td>
<td>7</td>
<td>34</td>
<td>bvFTD</td>
<td>Personality change</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>14/F/56†</td>
<td>7</td>
<td>32</td>
<td>bvFTD</td>
<td>Personality change, executive dysfunction, memory loss</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>15/F/61†</td>
<td>NA</td>
<td>NA</td>
<td>Semantic dementia</td>
<td>Comprehension problems, difficulty with naming of people, places, and things</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>16/F/56†</td>
<td>NA</td>
<td>NA</td>
<td>bvFTD</td>
<td>Executive dysfunction</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: bvFTD, behavioral-variant frontotemporal dementia; CBS, corticobasal syndrome; L, left; MR, magnetic resonance; NA, not applicable; R, right; STMS, Short Test of Mental Status; +, present; –, absent.

*Based on consensus criteria.†Still alive.

PATHOLOGICAL ANALYSIS

All case specimens had undergone extensive neuropathological examination using routine and immunohistochemical stains as previously described in detail. A pathological diagnosis of FTLD-U was made on the basis of the finding of neuronal loss, spongiosis, and gliosis in the frontotemporal neocortex consistent with frontotemporal lobar degenerative changes, as well as the presence of ubiquitin-positive intraneuronal inclusions and neurites in the neocortex or in the dentate granule cell layer of the hippocampus. Any case with evidence of motor neuron disease was excluded as previously described.

GENETIC ANALYSIS

The 12 coding exons of PGRN were amplified by polymerase chain reaction (PCR) using previously published primers and protocol. Novel PCR primers flanking the noncoding exon 0 and 3' untranslated region of PGRN were also developed. Standard 25-µL PCR reactions were performed using commercially available PCR products (Qiagen, Valencia, Calif) and a final concentration of 0.8µM for each primer. The PGRN exon 0 and 3' untranslated region fragments were cycled using touchdown protocols of 70°C to 55°C and 58°C to 48°C, respectively. The PCR products were purified using filtration plates (MultiScreen; Millipore, Billerica, Mass) and were sequenced in both directions on a sequence detection system (ABI 3730 with Big Dye chemistry; Applied Biosystems, Foster City, Calif) according to the manufacturer's protocol. Genomic characterization of PGRN was performed as previously described.

Magnetic resonance imaging studies were performed at 1.5 T using a standardized imaging protocol that included a coronal
RESULTS

SUBJECTS

Table 1 gives the clinical features of the PGRN-positive and PGRN-negative groups. Most subjects had a clinical diagnosis of bvFTD, although 2 subjects in each group had a diagnosis of semantic dementia or CBS. A comparison of the demographic features between the groups is given in Table 2. There was no significant difference in the sex ratio or age at the time of MR imaging across the 3 groups. In addition, there was no significant difference between the PGRN-positive and PGRN-negative subjects in age at disease onset, illness duration, time from disease onset to MR imaging, or Short Test of Mental Status score at the time of MR imaging. All subjects were white and non-Hispanic. All PGRN-positive subjects had an autosomal dominant pattern of inheritance; only 2 PGRN-negative subjects had any suggestion of an autosomal dominant family history. Additional clinical features developed after the time of MR imaging (Table 1). The PGRN-positive subjects were more likely to develop language impairment (90% vs 20%; P = .03) and parkinsonism (90% vs 30%; P = .05) compared with the PGRN-negative subjects before death.

MUTATIONS

Sequencing analyses showed that 5 different PGRN mutations were present in our cohort. These included c154delA (pThr52HisfsX2), c910_911insTG (pTrp304LeufsX58), c1395_1396insC (pCys466LeufsX46), c1145del1C (pThr382SerfsX30), and c138 + 1G→A (IVS1 + 1G→A).

VBM ANALYSIS

The PGRN-positive group showed a widespread and severe pattern of gray matter loss compared with the control group (Figure 1). The most severe regions of gray matter loss were observed in the inferior and middle frontal gyri, medial frontal lobe, temporal lobes, and parietal lobes. The patterns of gray matter loss were bilateral, although the frontal and parietal lobe loss seemed to be slightly greater in the right hemisphere. In comparison, the regions of gray matter loss identified in the PGRN-negative group were restricted to the temporal and frontal lobes. The patterns of gray matter loss were less severe than those observed in the PGRN-positive subjects. The temporal lobe loss spread from the anterior temporal pole back to involve the medial and inferior temporal regions and the posterior inferior temporal gyri. The frontal lobe loss was observed in the medial frontal cortex, inferior and middle frontal gyri, and orbitofrontal cortex. The insula was also involved. As in the PGRN-positive group, the frontal lobe loss was slightly greater in the right hemisphere.

A direct statistical comparison was performed between the 2 groups (Figure 2). The PGRN-positive group showed significantly greater gray matter loss in the superior frontal lobes and parietal lobes, predominantly on the right, than the PGRN-negative group (uncorrected P < .01). No regions showed greater involvement in the PGRN-negative group compared with the PGRN-positive group.

COMMENT

This study demonstrated differences in the severity and distribution of gray matter atrophy and clinical variations in FTLD-U cases with and without PGRN mutations. Because both groups had an identical pathological diagnosis of FTLD-U and were matched for clinical diagnosis, we had hypothesized that the patterns of atrophy would be similar in subjects with and without PGRN mutations. However, our findings demonstrated differences between the PGRN-positive and PGRN-negative groups. The PGRN-negative subjects showed a pattern of temporal and frontal lobe volume loss, as previously

Table 2. Demographics of Subjects

<table>
<thead>
<tr>
<th>Demographic</th>
<th>PGRN-Positive Group (n = 8)</th>
<th>PGRN-Negative Group (n = 8)</th>
<th>Control Subjects (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>4:4</td>
<td>2:6</td>
<td>6:10</td>
</tr>
<tr>
<td>Age at disease onset, y</td>
<td>60.1 ± 6.6</td>
<td>64.5 ± 9.5</td>
<td>62.4 ± 6.9</td>
</tr>
<tr>
<td>Illness duration, y</td>
<td>6.7 ± 1.0</td>
<td>6.7 ± 1.0</td>
<td>7.5 ± 4.0</td>
</tr>
<tr>
<td>Time from disease onset to MR imaging, y</td>
<td>2.7 ± 1.0</td>
<td>3.2 ± 1.9</td>
<td>NA</td>
</tr>
<tr>
<td>STMS score at the time of MR imaging‡</td>
<td>28.1 ± 4.5</td>
<td>29.4 ± 3.8</td>
<td>36.3 ± 2.2</td>
</tr>
</tbody>
</table>

Abbreviations: MR, magnetic resonance; NA, not applicable; STMS, Short Test of Mental Status.
*Data are given as mean ± SD unless otherwise indicated.
†Illness duration (time from disease onset to death) was available for 6 PGRN-positive subjects who have died.
‡Available for 7 PGRN-positive subjects and 7 PGRN-negative subjects.
reporting in FTLD-U. However, the PGRN-positive subjects showed a more severe and widespread pattern of gray matter loss than the PGRN-negative subjects. The most severe regions of loss were identified in the temporal and frontal lobes and in the parietal lobe, which was spared in the PGRN-negative group. A direct comparison between the 2 groups showed that the PGRN-positive subjects had a greater degree of frontal and parietal atrophy than the PGRN-negative subjects. The fact that these results did not persist after correction for multiple comparisons most likely reflects the heterogeneity in each group. Similarly, our recent pathological findings demonstrated significantly lower mean ± SD brain weights at death in PGRN-positive subjects compared with PGRN-negative subjects (902 ± 160 vs 1030 ± 140 g; \( P = .007 \)) and showed greater atrophy of the frontal and parietal lobes in the PGRN-positive subjects. Furthermore, another pathological study found that the frontal lobes were the most severely affected regions in PGRN-positive subjects, although the temporal and parietal lobes were also affected. Single-subject MR images have shown frontal, temporal, and parietal atrophy in PGRN-positive subjects. Although VBM provides a group-level analysis and the findings should not be generalized to single subjects, our results suggest that a severe pattern of atrophy affecting the temporal and parietal and especially the frontal lobes may be indicative of an underlying PGRN mutation. Therefore, it is possible that the mutation results in a more malignant form of FTLD-U. A recent case study reported a rate of brain atrophy of more than 3.3% per year in a PGRN-positive subject. This may reflect differences between familial and sporadic forms of FTLD-U because most of the PGRN-negative subjects had no autosomal dominant family history. Greater severity of Alzheimer disease pathological features is found in genetically determined familial Alzheimer disease, and MR imaging studies have demonstrated that younger-onset familial cases of Alzheimer disease show more widespread patterns of atrophy compared with older-onset sporadic cases.

Although there were differences between the PGRN-positive and PGRN-negative groups, they both showed involvement of the temporal lobe, particularly the posterior temporal gyri. In 2 previous VBM studies, a region of severe gray matter loss affecting the posterior temporal lobe in subjects with FTLD-U was identified, and it was hypothesized that this might be a signature pattern of this pathological condition. Findings from this study concur with those results and further suggest that the signature pattern is related to the pathological features of FTLD-U and is perhaps independent of the genetic cause of the disease.

The pattern of gray matter loss in the PGRN-positive subjects was symmetric, although with slightly greater involvement of the right frontal lobe. However, the lateralization observed in the PGRN-positive subjects may be associated with the particular subjects and the particular clinical diagnoses included in this analysis. Some ongoing MR imaging investigations at our institution among a larger number of PGRN-positive subjects show greater involvement of the right hemisphere in some, whereas others show the opposite pattern (C.R.J., un-
published data, 2006). Previous studies reporting on single-subject MR images noted left-sided\textsuperscript{18} and right-sided\textsuperscript{16,19} PGRN-positive subjects. Therefore, although asymmetry seems to be a feature of the mutation, there appears to be no particular dominant hemisphere.

In our series of PGRN-positive subjects, bvFTD was more prevalent than other syndromes, occurring in 75\% of subjects. This is similar to the frequency typically reported in FTLD-U.\textsuperscript{2} Our patients presented with personality change, abulia, loss of attention, and executive dysfunction. Furthermore, bvFTD has been described in other clinical investigations of PGRN\textsuperscript{16,18} and was found to be the most prevalent clinical diagnosis.\textsuperscript{16} One of our subjects had a diagnosis of CBS\textsuperscript{23} at the time of MR imaging, which has been described in another family with PGRN mutations.\textsuperscript{17} Our subject had been diagnosed as having idiopathic Parkinson disease before being seen at our institution. Therefore, in patients with an initial diagnosis of idiopathic Parkinson disease and an autosomal dominant family history, a PGRN mutation should be considered. The other subject with aphasia in our cohort had features consistent with semantic dementia.\textsuperscript{1} This subject had a fluent aphasia with prominent anomia and comprehension problems. This finding is different from the results of previous PGRN studies\textsuperscript{15,18} in which aphasia was more consistent with the progressive nonfluent aphasia variant of FTLD-U. The PGRN-negative subjects were matched to the PGRN-positive subjects for syndromic diagnosis; 75\% had bvFTD, with 1 each having CBS and semantic dementia. As in the PGRN-positive subjects with bvFTD, the PGRN-negative subjects had personality changes, apathy, anhedonia, and executive dysfunction. The PGRN-negative subject with semantic dementia had anomia aphasia, circumlocutions, and behavioral changes.\textsuperscript{1}

Although our subjects were matched by clinical syndromes at the time of MR imaging and showed no differences in clinical severity or illness duration, the PGRN-positive subjects were more likely to develop language impairment (90\%) and parkinsonism (90\%) later in the disease course than the PGRN-negative subjects (20\% of whom developed language impairment and 30\% of whom developed parkinsonism). However, the prevalence of behavioral features was similar among the PGRN-positive (75\%) and PGRN-negative (88\%) groups. Therefore, the later development of significant parkinsonism and language impairment in subjects with an autosomal dominant family history may be a clue to the presence of a PGRN mutation and should prompt the physician to consider genetic screening. Language impairment and parkinsonism were also more common in the PGRN-positive subjects in our pathological investigation that included a somewhat different cohort.\textsuperscript{14} In some of those subjects, Lewy bodies were found, which further supports the importance of considering PGRN mutations in autosomal dominant familial Parkinson disease or in subjects in whom parkinsonism is a significant feature. Language impairment was variable, with the development of features of expressive and receptive deficiencies. The PGRN-positive subjects frequently became mute. Given the more widespread volume of gray matter loss seen in the PGRN-positive subjects, these developments are of no surprise. We hypothesize the following 2 scenarios:

\begin{enumerate}
\item [(1)] anatomical structures involved with the development of parkinsonism and aphasia eventually become affected in PGRN-positive subjects or
\item [(2)] the anatomical structures are already affected given the widespread atrophy, but there exists a threshold effect whereby there has to be a certain amount of pathway or anatomical destruction present before the clinical features emerge.
\end{enumerate}

The major strengths of this study were that the PGRN-positive and PGRN-negative groups were matched in terms of clinical and pathological diagnoses and demographic features. The technique of VBM is unbiased and allows an assessment of gray matter loss across the whole brain without having to make a priori assumptions concerning which structures to assess. The limitations include the fact that the number of subjects in each group was small. However, it is difficult to find subjects with a PGRN mutation, an artifact-free MR image acquired using a standardized protocol, and an autopsy-confirmed diagnosis of FTLD-U. Despite the small numbers, we observed well-defined patterns of gray matter loss that correlate closely to previously published findings in larger groups of subjects with FTLD-U.\textsuperscript{12,13} The results also closely match our recent pathological findings in PGRN-positive sub-
subjects. However, our cohort represented only 5 different PGRN mutations, therefore, the results may not be generalizable to subjects with other PGRN mutations.

In summary, the findings from this study suggest that PGRN mutations may be associated with more severe patterns of cerebral atrophy, particularly involving the frontal and parietal lobes, in subjects with FTLD-U. The subjects with PGRN mutations developed more parkinsonism and language impairment than the PGRN-negative subjects. It will be important for these results to be validated and correlated with detailed clinical information in a larger group of subjects.

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