

# Clinical, Genetic, and Pathologic Characteristics of Patients With Frontotemporal Dementia and Progranulin Mutations

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**Background:** Patients with frontotemporal dementia due to mutation of progranulin may have a distinct phenotype.

**Objective:** To identify distinct clinical and pathologic features of patients with frontotemporal dementia who have mutations of progranulin (GRN).

**Design:** Retrospective clinical-pathologic study.

**Setting:** Academic medical center.

**Patients:** Twenty-eight patients with frontotemporal dementia, including 9 with GRN mutations (4 autopsy cases and 5 with only clinical information) and 19 with the identical pathologic diagnosis—frontotemporal lobar degeneration with ubiquitin-positive and tau-negative inclusions (FTLD-U)—and no GRN mutations.

**Main Outcome Measures:** Demographic, symptom, neuropsychological, and autopsy characteristics.

**Results:** Patients with and without a GRN mutation have similar demographic features, although family history is significantly more common in patients with frontotemporal dementia and a GRN mutation. Both patient groups have frequent social and personality complaints. Neuropsychological evaluation reveals a significant recognition memory deficit in patients with a GRN mutation but a significant language deficit only in patients without a GRN mutation. At autopsy, the semiquantitative burden of ubiquitin abnormality is relatively modest in both groups of patients.

**Conclusion:** Patients with a GRN mutation differ clinically from those with the same pathologic diagnosis but no GRN mutation.

*Arch Neurol.* 2007;64(8):1148-1153

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**F**rontotemporal dementia (FTD) typically presents in the fifth or sixth decade of life<sup>1,2</sup> and occurs almost as commonly as Alzheimer disease in patients younger than 65 years.<sup>3,4</sup> A strong family history of cognitive and psychiatric complaints is present in many patients with the clinical diagnosis of FTD.<sup>5-8</sup> Some cases with an FTD phenotype are due to mutations in microtubule-associated protein tau (*MAPT*) on chromosome 17, valosin-containing protein (*VCP*) on chromosome 9, and chromatin modifying protein 2B (*CHMP2B*) on chromosome 3. Several families with hereditary FTD were known to show linkage to chromosome 17, but no mutations in *MAPT* had been identified.<sup>9,10</sup> This led investigators to examine neighboring genes. Two research groups recently described the association of mutations in the gene coding for progranulin (*GRN*), also located on the q21 portion of chromosome 17, with FTD.<sup>11,12</sup> Published clinical characterizations of these patients provide the spec-

trum of the phenotype, but there is limited quantitative neuropsychological evaluation and no informative control group.<sup>13-15</sup> In this study we examine clinical, quantitative neuropsychological, and pathologic characteristics of patients with a GRN mutation and contrast these cases with individuals who have the identical microscopic histopathologic abnormality but who do not have a mutation in GRN.

The 2 major presenting characteristics of FTD include primary progressive aphasia (PPA)<sup>16,17</sup> and a disorder of social comportment and executive functioning (SOC/EXEC).<sup>18,19</sup> Primary progressive aphasia may include progressive nonfluent aphasia, involving effortful and agrammatic speech output with apraxia of speech and grammatical comprehension difficulty. Another form of PPA involves semantic dementia, a disorder of single word comprehension and object knowledge that is due to degradation of the underlying conceptual knowledge. Some SOC/EXEC patients are passive owing to apathy, lack of initiative, distractibility, and poor social and cognitive organi-

zation, whereas others are disinhibited, hypersexual, hyperoral, rigidly compulsive, and lacking empathy. These features of FTD also can be seen in a form of motor neuron disease with dementia,<sup>20,21</sup> and more recently there have been several articles<sup>22,23</sup> documenting subtler forms of cognitive difficulty in many patients with motor neuron disease who do not have obvious dementia. Progressive aphasia and a social disorder are reported in association with *GRN* mutations,<sup>13-15</sup> although these syndromes can change over time.<sup>24</sup> Characterizations such as these are useful in understanding the phenotype associated with *GRN* mutations, but quantitative neuropsychological evaluations would add another important dimension to the clinical characterization of these patients.

The histopathologic picture underlying FTD is broadly partitioned into 2 groups, one with pathologic tau inclusions and the second lacking tau inclusions.<sup>25,26</sup> Conditions with tau-immunoreactive neuronal inclusions include dementia with Pick bodies, argyrophilic grain disease, corticobasal degeneration, and progressive supranuclear palsy. The tau-negative conditions can be further subdivided into those with no identifiable inclusions, known as dementia lacking distinctive histopathologic characteristics,<sup>27</sup> and the more common finding, frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U),<sup>28</sup> which is identical to the pathologic characteristics seen in motor neuron disease. All reported patients with a *GRN* mutation seem to have FTLD-U pathologically, but not all patients with FTLD-U have a *GRN* mutation. In this study we contrast a cohort of patients with *GRN* mutations with patients who have the identical FTLD-U pathologic diagnosis causing FTD but have a normal *GRN* gene.

## METHODS

### PATIENTS

Twenty-eight patients with FTD were evaluated in this study. Twenty-three patients had an autopsy diagnosis of FTLD-U, 4 with a mutation in *GRN*. An additional 5 living patients were included for the clinical correlations on the basis of having a *GRN* mutation. All of the patients' conditions were diagnosed by experienced physicians at the University of Pennsylvania based on informant interview, medical history, neurologic examination, neuropsychological evaluation, laboratory screening, and brain imaging when available (including magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography). Because the patients were accrued from multiple clinics by different investigators across a 10-year period, there was some variability in the clinical data obtained and the approach to clinical diagnosis. Demographic characteristics are summarized in **Table 1**. Disease duration (survival) was computed from the time of symptom onset until the time of death in autopsy-confirmed patients. Symptom onset was based on family report of the earliest persistently abnormal clinical feature in the domains of language, social and personality, memory, executive, visuospatial, and motor functioning. The time of initial diagnosis at the University of Pennsylvania was not used because patients were often referred after a widely varying period during which previous opinions had been rendered.<sup>29</sup>

Symptoms tabulated at presentation included social and behavioral changes, language dysfunction, other cognitive deficits (eg, memory loss, inattention, planning disorder, and visuospatial complaints), movement disorder, and focal weakness.

**Table 1. Clinical and Demographic Characteristics of *GRN* Mutation-Positive Patients Compared With Patients With FTLD-U Without a *GRN* Mutation**

Characteristic	Patients With <i>GRN</i> Mutations (n=9)	Patients With FTLD-U (n=19)
Sex, F/M, No.	5/4	10/9
Pathologic evaluation, No.	4 <sup>a</sup>	19
Clinical diagnosis, No.		
ALS	0	1
Other	1	2
FTD	8	16
Clinical FTD phenotype, No.		
Progressive nonfluent aphasia	1	2
Semantic dementia	0	3
Progressive mixed aphasia	1	2
Social-executive disorder	6	9
Demographics, mean (SD)		
Age at onset, y	55.0 (10.4)	59.8 (9.7)
Age at testing, y	60.1 (6.1)	63.5 (10.2)
Education, y	15.8 (3.3)	14.2 (2.5)
Disease duration, mo	79.0 (13.6) <sup>a</sup>	78.1 (42.1)
Family history, No. (%) <sup>b</sup>	7 Families (9 individuals)	15 Families evaluated
Definite	1 (14)	0
Probable	2 (29)	1 (7)
Possible	3 (43)	3 (20)
None	0	7 (47)
Unknown	1 (14)	4 (27)
significance		

Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; FTLD-U, frontotemporal lobar degeneration with ubiquitin-positive and tau-negative inclusions; *GRN*, progranulin.

<sup>a</sup>Four patients with a *GRN* mutation were evaluated at autopsy.

<sup>b</sup>Pedigrees and family medical histories were evaluated and were classified into the categories shown based on the number of affected individuals and their relationships in a 3-generation family pedigree. Family history was available in only 15 patients without a *GRN* mutation and combined with FTLD-U at autopsy.

A limited battery of neuropsychological measures was obtained on a large subset of patients, including a measure of general cognitive functioning (Mini-Mental State Examination: a 30-point scale surveying dementia severity); measures of executive functioning (digit span forward: the longest series of numbers repeated correctly in the presented order; digit span reverse: the longest series of numbers repeated correctly in the reverse order of presentation; and category naming fluency: the number of different animals named in 60 seconds); a measure of language (confrontation naming: correct confrontation naming of black-and-white line drawings from an abbreviated version of the Boston Naming Test); measures of memory (memory delay: correct recall of 10 words after a brief delay following presentation during 3 learning trials; and memory recognition: correct recognition of the 10 words interspersed among 10 foils, probed after delayed recall); a measure of visuospatial functioning (visual constructions: an 11-point scale rating the accurate copying of 4 geometric designs); and a measure of social functioning (social scale: a 7-point scale surveying disorders of social comportment and personality).

### DNA SEQUENCE ANALYSIS OF *GRN*

Genomic DNA from the 28 studied patients was prepared from peripheral blood or brain tissue according to standard procedures.

Exons 1-12 of *GRN* were amplified using flanking intronic primers as previously described.<sup>11</sup> Amplification reactions (50  $\mu$ L) for exons 1-3 and 7-12 were performed using AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, California) and 200nM (final concentration) each primer. The touchdown protocol consisted of 95°C (10 minutes), followed by 14 cycles of 95°C (30 seconds), 58°C with a reduction of 0.5°C per cycle (30 seconds), 72°C (1 minute), and 20 cycles of 95°C (30 seconds), 51°C (30 seconds), 72°C (1 minute), with a final 5-minute extension. Exons 4 and 5 were amplified together using ReddyMix PCR Master Mix (ABgene Ltd, Epsom, England) and the same conditions as for the other exons except the initial denaturation step, which was for 2 minutes at 95°C. Amplification products were purified using AMPure (Agencourt Bioscience Corp, Beverly, Massachusetts), followed by a single-pass bidirectional polymerase chain reaction sequencing procedure, which was performed by Agencourt Bioscience. Results were analyzed using a software program (Mutation Surveyor; SoftGenetics LLC, State College, Pennsylvania). All variants were confirmed by means of repeated sequencing.

## PATHOLOGIC EVALUATION

Twenty-three patients, including 4 with a *GRN* mutation, underwent pathologic evaluation in the Center for Neurodegenerative Disease Research at the University of Pennsylvania and were selected on the basis of the pathologic diagnosis of FTL-D-U. The 19 patients with normal *GRN* and FTL-D-U pathologic characteristics had sufficient clinical and cognitive information to be informative as a contrast group for the patients with FTL-D-U with a *GRN* mutation and matched the demographic features of the 4 patients with a *GRN* mutation. All autopsy cases were identified from the consecutive pathologic series collected between January 1, 1995, and December 31, 2006, at the Center for Neurodegenerative Disease Research. As described in detail elsewhere,<sup>25</sup> the neuropathologic diagnoses were established by examining representative blocks from brain. Routinely applied histochemical methods included hematoxylin-eosin and thioflavin S stains supplemented with silver (Bielschowsky and Gallyas), Luxol-fast blue, and Congo red stains. In addition, immunohistochemical analysis was routinely performed following standard and previously published protocols with antibodies that detect specific neurodegenerative lesions, including antibodies to phosphorylated tau (PHF1<sup>30</sup>),  $\beta$ -amyloid (ie, 4G8) (Senetek, Maryland Heights, Missouri),  $\alpha$ -synuclein (Syn303<sup>31</sup>), ubiquitin (Chemicon International, Temecula, California, and Dako Cytomation, Glostrup, Denmark), phosphorylated NF subunits (RMO24<sup>32</sup>), and  $\alpha$ -internexin (Zymed Laboratories, San Francisco, California).

All of the cases were reviewed by 2 board-certified neuropathologists (M.S.F. and J.Q.T.) in a manner blinded to their clinical diagnosis, and consensus pathologic diagnoses were established according to the Work Group on Frontotemporal Dementia and Pick's Disease.<sup>26</sup> In addition, all of the cases were further evaluated to rule out other potentially contributing neurologic disorders. Using established criteria,<sup>26,33-37</sup> these brains showed the presence of ubiquitin-positive and tau/ $\alpha$ -synuclein-negative inclusions (ie, FTL-D-U). All cases without any inclusions were classified as dementia lacking distinctive histopathologic characteristics and were excluded from this study. Eight regions were analyzed, including cortex (middle frontal gyrus, inferior parietal lobule, superior and middle temporal gyri, and anterior cingulate gyrus), limbic system (hippocampus, amygdala, and entorhinal cortex), and subcortical nuclei (basal ganglia with nucleus basalis and substantia nigra). Semiquantitative methods similar to those described for senile plaques in Alzheimer disease<sup>38</sup> (ie, absent, low, moderate, and high) were used to assess the density of immunostained ubiquitin lesions

in these regions. Grading was assigned values of 0 to 3 (0=no or rare pathology, 1=low pathology, 2=moderate pathology, and 3=high pathology) in each analyzed brain region.

## STATISTICAL ANALYSES

Nonparametric statistical tests, such as Mann-Whitney and Friedman tests, were used to evaluate demographic characteristics, frequencies of clinical features, neuropsychological performance, and severity of the histopathologic abnormalities. Neuropsychological measures were converted to *z* scores in each individual relative to 25 age- and education-matched healthy control subjects, and *P* = .01 (equivalent to a *z* score of -2.32) was the threshold set to establish a significant impairment. The Mini-Mental State Examination is scored on a scale from 30 (normal) to 0 (severely impaired), and social disorder is scored as the average social severity prorated to a scale ranging from 1.0 (normal) to 0.0 (severely impaired).

## RESULTS

Pathogenic mutations in *GRN* were identified in 9 studied individuals representing 7 families (**Table 2**). Two of the mutations, p.R110X and p.Q337X, have not been previously described but are presumed to be pathogenic because they create nonsense mutations resulting in a premature stop codon.

The demographic characteristics of *GRN* mutation-positive patients (4 with FTL-D-U pathologic characteristics at autopsy and 5 with clinical FTD) and patients with FTL-D-U without a *GRN* mutation are summarized in Table 1. Age at onset in patients with a *GRN* mutation ranges from 37 to 72 years. There is no statistically significant difference in age at onset, disease duration, or sex between patients with a *GRN* mutation and patients without a *GRN* mutation and the histopathologic diagnosis of FTL-D-U.

The syndromic diagnoses of these patients are summarized in Table 1. The spectrum of clinical diagnoses in patients with and without a *GRN* mutation is similar, although a positive family history is more common in patients with a *GRN* mutation. Family histories were classified as definite, probable, possible, or none regarding the likelihood of having a genetic basis for the disease; a category of unknown significance was used when the family history data available were sparse or questionable. The classification results are given in Table 1. Of families with a *GRN* mutation, 86% have some (1 definite, 2 probable, and 3 possible) family history of a similar condition as the proband, and there are none without a family history. In contrast, only 27% of patients with FTL-D-U without a *GRN* mutation have some family history (1 probable and 3 possible), whereas 47% have no family history ( $\chi^2_1 = 11.27$ ; *P* < .001).

Clinical features at presentation are summarized in **Table 3**. Patients and accompanying families with a *GRN* mutation and patients with FTL-D-U and accompanying families without a *GRN* mutation frequently complain of social and language disorders. There are moderate levels of executive and memory complaints in both groups as well. Neither group complains of visuospatial difficulties. A Friedman test shows a difference between groups in terms of the pattern of complaints ( $\chi^2_6 = 51.44$ ; *P* < .001). In patients

**Table 2. Summary of Pathogenic *GRN* Mutations Identified in 7 Families**

Patient No.	Clinical Diagnosis or FTLD-U Autopsy <sup>a</sup>	Genomic Mutation <sup>b</sup>	Predicted cDNA <sup>c</sup>	Predicted Protein <sup>d</sup>	Location
1	FTD clinical	g.1080903C→T	c.328C→T	p.R110X <sup>e</sup>	EX3
2	FTD clinical	g.1081940-1081941delCA	c.675delCA	p.Ser226TrpfsX28	EX6
3	FTLD-U	g.1082611G→A	c.911G→A	p.W304X	EX8
4	FTLD-U	g.1082798C→T	c.1009C→T	p.Q337X <sup>e</sup>	EX9
5A	FTD clinical	g.1083260C→T	c.1252C→T	p.R418X	EX10
5B	FTLD-U	g.1083260C→T	c.1252C→T	p.R418X	EX10
6A	FTD clinical	g.1083577C→T	c.1477C→T	p.R493X	EX11
6B	FTD clinical	g.1083577C→T	c.1477C→T	p.R493X	EX11
7	FTLD-U	g.1083577C→T	c.1477C→T	p.R493X	EX11

Abbreviations: cDNA, complementary DNA; EX, exon; FTD, frontotemporal dementia; FTLD-U, frontotemporal lobar degeneration with ubiquitin-positive and tau-negative inclusions; *GRN*, progranulin.

<sup>a</sup>All 9 patients were evaluated clinically, some by using extensive neuropsychological measures. Four patients were evaluated neuropathologically and had a diagnosis of FTLD-U (patients 3, 4, 5B, and 7). The patient number designations with A and B indicate that these individuals are related.

<sup>b</sup>Genomic numbering is according to GenBank NT\_010783.

<sup>c</sup>Predicted cDNA numbering is according to GenBank NM\_002087.2.

<sup>d</sup>Predicted protein numbering is according to GenPept NP\_002078.1.

<sup>e</sup>Novel *GRN* variants described in this article are indicated.

**Table 3. Patients With Clinical Complaints When First Seen**

Complaint	Patients With <i>GRN</i> Mutations, No. (%) (n=9)	Patients With FTLD-U, No. (%) (n=19)
Social	6 (67)	14 (74)
Language	4 (44)	12 (63)
Executive	4 (44)	5 (26)
Memory	2 (22)	5 (26)
Visuoperceptual	1 (11)	0
Motor-pyramidal	0	2 (11)
Motor-extraparapyramidal	3 (33)	2 (11)

Abbreviations: FTLD-U, frontotemporal lobar degeneration with ubiquitin-positive and tau-negative inclusions; *GRN*, progranulin.

with *GRN* mutations, complaints about social, executive, and language difficulties are more common than motor complaints ( $P < .05$ , Mann-Whitney tests). There is a trend toward social, executive, and language complaints being more common than visuoperceptual complaints ( $P < .08$ ). In patients with FTLD-U without a *GRN* mutation complaints of a social disorder are significantly more common than complaints of executive, memory, visual, and motor difficulties (each contrast is significant at least at the  $P < .01$  level). Mann-Whitney tests also show that language complaints are more common in patients with FTLD-U without a *GRN* mutation than executive, visual, and motor complaints and that executive complaints are more common than visual complaints (each contrast is significant at least at the  $P < .05$  level).

The *GRN* mutation group and the FTLD-U group with no mutation show distinct profiles of relative cognitive difficulty. **Table 4** summarizes the neuropsychological evaluation. At the time of evaluation, the groups with and without *GRN* mutations did not differ statistically in age or disease duration. The patient groups also did not differ significantly in their overall dementia severity, as measured using the Mini-Mental

**Table 4. Neuropsychological Performance of *GRN*-Positive and FTLD-U *GRN*-Negative Patients<sup>a</sup>**

Task (Available Scores) <sup>b</sup>	Patients With <i>GRN</i> Mutations	Patients With FTLD-U
MMSE (n=24)	25.1 (3.5)	21.8 (7.4)
Digit span forward (n=13) <sup>c</sup>	-1.17 (1.3)	-0.79 (1.5)
Digit span backward (n=12) <sup>c</sup>	-1.31 (1.6)	-0.88 (2.0)
Category naming fluency (n=16) <sup>c</sup>	-1.38 (0.9)	-2.98 (0.7)
Confrontation naming (n=13) <sup>c</sup>	-0.12 (1.1)	-5.59 (2.3)
Memory recall (n=16)	-1.45 (1.8)	-1.83 (1.6)
Memory recognition (n=14)	-4.24 (4.9)	-2.11 (2.9)
Visual constructions (n=14)	0.59 (0.0)	-0.42 (1.5)
Social scale (n=22)	0.34 (0.23)	0.40 (0.23)

Abbreviations: FTLD-U, frontotemporal lobar degeneration with ubiquitin-positive and tau-negative inclusions; *GRN*, progranulin; MMSE, Mini-Mental State Examination.

<sup>a</sup>All data are mean (SD) z scores relative to 25 age- and education-matched controls, except the raw score of the MMSE (maximum score=30) and the social scale (maximum score=1.00). Mean (SD) disease duration at the time of testing: *GRN*-positive cases, 49.2 (46.0) months; FTLD-U no mutation, 42.1 (34.3) months.

<sup>b</sup>Different numbers of scores are available because patients were seen by different physicians at different clinics or because a patient could not perform the task.

<sup>c</sup>Significant between-group differences were present for these measures at the  $P < .01$  level, according to the Mann-Whitney test.

State Examination. Nevertheless, using a z score criterion of -2.32 (equivalent to  $P < .01$ ), both groups show some difficulty with memory recognition performance relative to a group of age- and education-matched controls, but only patients with a *GRN* mutation exceed a threshold of statistically significant impairment. In comparison, only patients with FTLD-U without a *GRN* mutation are significantly impaired in their language functioning on measures of confrontation naming and category naming fluency guided by a semantic target ("animals"). Inspection of individual patient performance profiles reveals significant deficits in all but 1 (confrontation naming) or 2 (animal naming) patients with FTLD-U, but only 1 patient with a *GRN* mutation



**Table 5. Ubiquitin Neuropathologic Features in *GRN* and FTLD-U<sup>a</sup>**

Region (Available Samples)	Patients With <i>GRN</i> Mutations (n=4)	Patients With FTLD-U (n=19)
Mean ubiquitin (n=23)	1.03 (0.8)	1.41 (0.45)
Midtemporal cortex (n=23)	1.25 (1.0)	1.79 (0.9)
Entorhinal cortex (n=23)	1.50 (1.7)	2.05 (0.8)
Hippocampus (n=23)	1.00 (1.4)	1.47 (0.9)
Amygdala (n=19) <sup>b</sup>	0.00	1.44 (1.0)
Midfrontal cortex (n=23)	1.50 (1.3)	1.42 (0.8)
Parietal cortex (n=20)	0.33 (0.6)	1.18 (0.7)
Cingulate cortex (n=13)	0.00	1.18 (1.1)
Basal ganglia (n=19)	0.67 (1.2)	0.94 (0.9)

Abbreviations: FTLD-U, frontotemporal lobar degeneration with ubiquitin-positive and tau-negative inclusions; *GRN*, progranulin.

<sup>a</sup>The density of immunostained ubiquitin lesions in each analyzed brain region was graded as 0 (no or rare), 1 (low), 2 (moderate), or 3 (high). Data are given as mean (SD).

<sup>b</sup>Significantly greater ubiquitin pathologic characteristics are present in patients with FTLD-U compared with *GRN*-positive patients in the amygdala, according to the Mann-Whitney test ( $U=6.0$ ;  $P<.05$ ).

has significantly abnormal performance, and this is present on only 1 of these measures.

Relatively modest levels of histopathologic disease are evident in the brains of patients evaluated by an autopsy. The burden of ubiquitin abnormality in these patients is summarized in **Table 5**. The mean overall density of ubiquitin-immunoreactive pathologic lesions is graded as mild in patients with a *GRN* mutation and patients with FTLD-U without a *GRN* mutation. There is significantly greater ubiquitin disease burden in the limbic system of patients with FTLD-U without a *GRN* mutation, due in part to the very low level of disease in patients with a *GRN* mutation. Greater ubiquitin pathologic characteristics in the midfrontal region is seen in *GRN*-positive compared with *GRN*-negative brains, but this is not a statistically significant effect. Likewise, the mean  $\pm$ SD overall densities of tau-immunoreactive (*GRN*+:  $0.23 \pm 0.2$ ; *GRN*- FTLD-U:  $0.28 \pm 0.3$ ), amyloid-immunoreactive (*GRN*+:  $0.53 \pm 1.1$ ; *GRN*- FTLD-U:  $0.30 \pm 0.6$ ), and  $\alpha$ -synuclein-immunoreactive (*GRN*+:  $0.59 \pm 1.2$ ; *GRN*- FTLD-U:  $0.12 \pm 0.5$ ) disease are modest and do not differ between the 2 groups of FTLD-U brains.

## COMMENT

Recently described mutations in *GRN* on chromosome 17 have been associated clinically with an FTD syndrome and FTLD-U pathologic characteristics. There are some clinical features that seem to distinguish patient groups with a pathologic diagnosis of FTLD-U that either have or lack a *GRN* mutation. Patients with a *GRN* mutation are more likely to have a positive family history, although *GRN* mutation-positive patients otherwise resemble patients with FTLD-U but no *GRN* mutation in their demographic characteristics. Patients without a *GRN* mutation have language complaints more frequently, and they are significantly impaired on language measures, although these deficits are less evident in patients with a

*GRN* mutation. Patients with a *GRN* mutation instead have relative difficulty with memory recognition. No cases of motor neuron disease are reported thus far in patients with a *GRN* mutation. The *GRN* mutation-positive patients also resemble patients with FTLD-U in their modest burden of ubiquitin histopathologic characteristics.

Reported patients with *GRN* mutations have an age at onset and a disease duration that is not distinct from other patients with FTD. In a large Belgian series,<sup>12</sup> language difficulties were evident in 9 of the 11 symptomatic cases (82%).<sup>10</sup> Four of these cases were given the clinical diagnosis of progressive nonfluent aphasia, 3 had reduced spontaneous speech, and 1 each was said to have word-finding problems and poststroke aphasia. Only 1 case in this series had a disorder of social and executive functioning. There may have been a bias toward a particular presentation in this Belgian series owing to a founder effect linking most members of the cohort. Likewise, 2 PPA families have now been reported to have a *GRN* mutation.<sup>14</sup> We find instead that language complaints are not as common in the present series consisting of 9 individuals from 7 unrelated families. Likewise, 17 of 24 cases (71%) with available clinical diagnoses in a multicenter series based at Mayo Clinic carried the clinical diagnosis of FTD with a social and executive disorder, whereas only 7 cases had the clinical diagnosis of PPA.<sup>13</sup> A detailed description of 2 unrelated cases also finds a social disorder: a patient with "childish" behavior became emotionally inappropriate and mute, and a second patient also presented with a disorder of social comportment and developed apathy and hyperoral behavior.<sup>15</sup>

Individual patients with a *GRN* mutation in the present series may have a modest deficit on verbally mediated tasks, but the neuropsychological assessment does not reveal a significant language impairment in patients with a *GRN* mutation. Reported families with PPA thus are distinctive but do not necessarily represent the norm among patients with a *GRN* mutation. In comparison, patients with the identical pathologic condition (FTLD-U) but no *GRN* mutation have significant language difficulty. Working memory is said to be impaired in 2 reported cases with a *GRN* mutation,<sup>15</sup> although it is difficult to evaluate the meaningfulness of these descriptions because they are not quantified. We do not find a deficit for working memory in this series. The detailed description of the 2 cases with a *GRN* mutation are said to have normal memory.<sup>15</sup> We find a relative deficit for recognition memory in patients with a *GRN* mutation, although patients with FTLD-U without a mutation also have mild recognition memory difficulty.

Several caveats must be kept in mind when interpreting these results. Because these patients were accumulated from several clinics across many years, we could identify only a few neuropsychological measures administered to many patients, and more comprehensive assessment may demonstrate additional impairments. Although we contrasted mutation-positive *GRN* patients with a demographically matched control group of patients with FTD without a *GRN* mutation, we may not have found extensive language difficulty in the mutation-positive *GRN* cohort because of the disease duration at

the time of clinical evaluation. Negative clinical and pathologic findings must be interpreted cautiously because of the relatively small number of patients we studied and the limited anatomical range of tissue samples. In sum, a wide range of clinical and neuropsychological deficits are evident in patients with a GRN mutation, but this series shows a significant impairment in recognition memory, with relatively modest language deficits.

**Accepted for Publication:** January 22, 2007.

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**Author Contributions:** Dr Grossman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Van Deerlin, Trojanowski, Lee, and Grossman. *Acquisition of data:* Van Deerlin, Moore, Yuan, Clark, Neumann, Kwong, and Grossman. *Analysis and interpretation of data:* Van Deerlin, Wood, Moore, Forman, Neumann, and Grossman. *Drafting of the manuscript:* Van Deerlin, Trojanowski, Lee, and Grossman. *Critical revision of the manuscript for important intellectual content:* Van Deerlin, Wood, Moore, Yuan, Forman, Clark, Neumann, Kwong, and Grossman. *Statistical analysis:* Grossman. *Obtained funding:* Van Deerlin, Trojanowski, Lee, and Grossman. *Administrative, technical, and material support:* Van Deerlin, Wood, Moore, Yuan, Forman, Neumann, and Kwong. *Study supervision:* Van Deerlin.

**Financial Disclosure:** None reported.

**Funding/Support:** This work was supported in part by grants AG17586, AG15116, NS44266, and AG10124 from the National Institutes of Health and by the Dana Foundation.

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