Parietal Lobe Deficits in Frontotemporal Lobar Degeneration Caused by a Mutation in the Progranulin Gene

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Objective: To describe the clinical, neuropsychologic, and radiologic features of a family with a C31LfsX35 mutation in the progranulin gene (*PGRN*) (GenBank CCDS11483.1).

Design: Case series.

Patients: A large British kindred (DRC255) with a *PGRN* mutation was assessed. Affected individuals presented with a mean age of 57.8 years (range, 54-67 years) and a mean disease duration of 6.1 years (range, 2-11 years).

Results: All patients exhibited a clinical and radiologic phenotype compatible with frontotemporal lobar degeneration based on current consensus criteria. However, unlike sporadic frontotemporal lobar degeneration, parietal deficits, consisting of dyscalculia, visuoperceptual /visuospatial dysfunction, and/or limb apraxia, were a common feature, and brain imaging showed posterior extension of frontotemporal atrophy to involve the parietal lobes. Other common clinical features included language output impairment with either dynamic aphasia or nonfluent aphasia and a behavioral syndrome dominated by apathy.

Conclusion: We suggest that parietal deficits may be a prominent feature of *PGRN* mutations and that these deficits may be caused by disruption of frontoparietal functional pathways.

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FRONTOTEMPORAL LOBAR DEgeneration (FTLD) comprises a group of disorders that is characterized by focal atrophy of the frontal and temporal lobes. Three clinical syndromes are described by consensus criteria[1]: frontotemporal dementia (FTD), progressive nonfluent aphasia (PNFA), and semantic dementia. Frontotemporal dementia is characterized by early personality change and progressive behavioral symptoms. Progressive nonfluent aphasia presents with speech production difficulties. Semantic dementia characteristically presents with anomia, poor single-word comprehension, and fluent aphasia. These syndromes overlap clinically and radiologically with one another and with other neurodegenerative disorders, including corticobasal degeneration (CBD), progressive supranuclear palsy, and motor neuron disease.[2,3]

Approximately 30% to 50% of patients with FTLD have a family history of dementia with autosomal dominant inheritance.[4] A proportion of these families have a mutation in the tau gene (*MAPT*) on chromosome 17q21.1 (www.molgen.ua.ac.be/FTDMutations). However, tau mutations collectively account for approximately only 4% of all cases of FTLD and 25% of cases with a positive family history.[5,6] Recently, mutations in the progranulin gene (*PGRN*), located 1.7 megabases away from *MAPT* at 17q21.32, have been identified in families with tau-negative, ubiquitin-positive inclusions on neuropathologic examination (FTLD-U). More than 30 mutations have been detected to date[6-9] and together may account for approximately 5% to 10% of FTLD cases.[6] Initial descriptions suggest that *PGRN* mutations are particularly associated with PNFA[7,8]; however, the phenotype continues to be defined.

METHODS

We describe a large British family (DRC255) comprising 10 affected individuals in 3 successive generations with a clinical FTLD phenotype (**Figure 1**). Two of the affected individuals had a genetically confirmed *PGRN* mutation. Five of the family members were seen either in the Specialist Cognitive Disorders Clinic of the National Hospital for Neurology and Neurosurgery, London, England, or as part of a longitudinal study of patients "at-risk" for developing FTLD. We de-
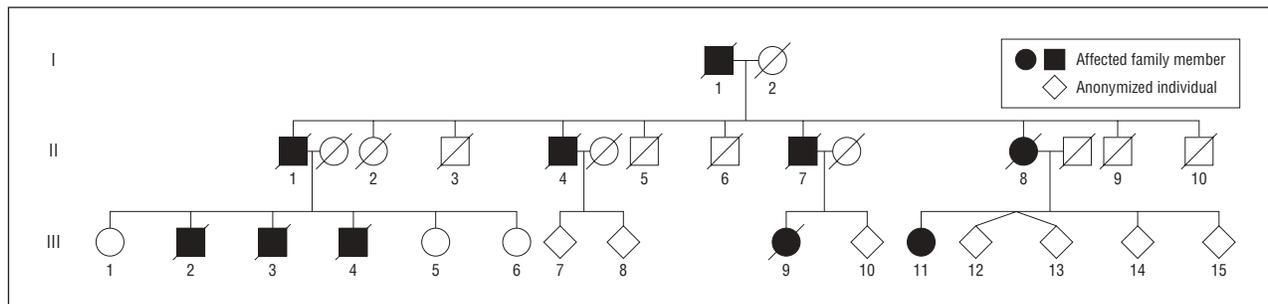
Figure 1. Pedigree of the DRC255 family.

scribe the clinical, neuropsychologic, radiologic, neuropathologic, and genetic findings in this family.

RESULTS

CLINICAL FEATURES

The average age at onset of disease in the family was 57.8 years (range, 54 to 67 years), and the mean length of clinical history from onset of symptoms to death was 6.1 years (range, 2 to 11 years). All affected family members developed a clinical syndrome characteristic of FTLD.

HISTORICAL CASES

Little information is available about family members from earlier generations. Patient I-1 died in his 50s with a diagnosis of presenile dementia. Patient II-1 died at the age of 56 years and was said to have both Pick disease and Parkinson disease on clinical grounds at the time of death. Patient II-4 was noted to have word-finding difficulties at the age of 56 years. He deteriorated cognitively over the next 2 years, with apraxia a prominent feature, and died at the age of 58 years. Patient II-7 was diagnosed as having presenile dementia at the age of 54 years and died at the age of 58 years. Patient II-8 developed a marked personality change in her mid-50s, becoming initially socially withdrawn and apathetic. Behavioral problems progressed, and she became mute before her death at the age of 66 years.

DETAILED CASE DESCRIPTIONS OF 5 AFFECTED INDIVIDUALS

Case III-2

A right-handed man developed behavioral symptoms and personality change at the age of 65 years. He initially became socially withdrawn and apathetic. Around the same time, his wife also noticed that he had lost empathy: he remained uncharacteristically indifferent after she fractured her arm. He developed a sweet tooth and hypersomnia, and his conversational speech diminished. Approximately 1 year into his illness, he developed route-finding problems and became disinhibited, making sexual advances to strangers. Eighteen months after symptom onset, he had difficulty putting clothes on correctly and was unable to perform simple calculations. He was first assessed 2 years into his illness, and, at that time, his Mini-

Mental State Examination (MMSE) score was 23/30.[10] Spontaneous speech was reduced, without evidence of aphasia. Neurologic examination revealed no abnormalities apart from brisk facial reflexes and mild bilateral ideomotor limb apraxia. A clinical diagnosis of FTD was made. The patient's condition continued to deteriorate and he died at the age of 72 years.

Case III-3

A 56-year-old man (handedness uncertain) presented with behavioral disturbance and language impairment. He became apathetic and hypersomnolent, stopped caring for himself, and displayed aggression toward family members. Around the same time, his speech decreased in quantity, with increasing use of "stock phrases." He was first assessed 2 years into his illness, at which time there was evidence of widespread cognitive impairment. His speech was reduced in quantity but without evidence of aphasia. Apart from a pout reflex, the findings of neurologic examination were unremarkable. A clinical diagnosis of FTD was made. Behavioral and speech problems progressed and were accompanied by difficulties with episodic memory. Four years into his illness, he was noted to be mute, with generalized rigidity. He died at the age of 64 years.

Case III-4

A 56-year-old left-handed man developed behavioral disturbance and language impairment. He became increasingly apathetic and aggressive, and the quantity of propositional speech diminished. Over the next year, he developed inappropriate social behavior, a sweet tooth, and hyperphagia. Two years into his illness, he had difficulties with episodic and topographic memory. The legibility of his writing deteriorated, and he had increasing difficulty with dressing and calculation. He was first assessed 2½ years into his illness, when his MMSE score was 10/30. He had little spontaneous speech and was echolalic, with verbal perseverations, but there were no phonemic, grammatical, or semantic errors. Neurologic examination revealed severe bilateral ideomotor and ideational limb apraxia. Parkinsonian features were present, with bradykinesia, rigidity, and postural tremor of both upper limbs, slightly more marked on the left side. There was a supranuclear gaze palsy, which affected upgaze. A clinical diagnosis of FTD was made. The patient died at the age of 61 years.

Table 1. Clinical Features in Affected Individuals

Variable	Case III-2	Case III-3	Case III-4	Case III-9	Case III-11
Sex, handedness	M, R	M, NK	M, L	F, R	F, R
Age at onset, y	65	56	56	58	67
Length of history (onset to death), y	7	8	5	5	NA
First symptoms	Apathy, decreased speech, loss of empathy, sweet tooth, and hypersomnia	Apathy, decreased speech, aggression, and hypersomnia	Apathy, decreased speech, aggression, and sweet tooth	Limb apraxia, dyscalculia, stuttering, anomia, and apathy	Anomia and apathy
Behavioral features					
Apathy	Yes	Yes	Yes	Yes	Yes
Loss of empathy	Yes	No	Yes	No	No
Disinhibition	Yes	No	Yes	No	No
Poor judgment	Yes	Yes	Yes	No	No
Aggression	Yes	Yes	Yes	No	No
Impaired insight	Yes	Yes	Yes	Yes	Yes
Sweet tooth	Yes	No	Yes	Yes	No
Hypersomnia	Yes	Yes	No	No	No
Language features					
Decreased quantity of speech	Yes	Yes	Yes	Yes	Yes
Echolalia	No	No	Yes	No	No
Hesitant or stuttering speech	No	No	No	Yes	No
Anomia	No	No	No	Yes	Yes
Agrammatism	No	No	No	No	Yes
Phonemic paraphasias	No	No	No	No	Yes
Mutism (years to mutism)	NK	Yes (4)	Yes (4)	Yes (2)	No
Other clinical findings					
Limb apraxia	Mild	NK	Mild	Severe	Mild
Ideational	No	NK	Yes	Yes	Yes
Ideomotor	Yes	NK	Yes	Yes	Yes
Parkinsonism	No	Yes (late)	Yes (late)	Yes (early)	No
Symmetry	No	R = L	L > R	L > R	No
Rigidity	No	Yes	Yes	Yes	No
Bradykinesia	No	No	Yes	No	No
Tremor	No	No	Yes	Yes	No
Pyramidal signs	No	No	No	Yes	No
Abnormal eye movements	No	No	Yes	Yes	No
Clinical diagnosis	FTD	FTD	FTD	CBD/PNFA	PNFA

Abbreviations: CBD, corticobasal degeneration; F, female; FTD, frontotemporal dementia; L, left; M, male; NA, not applicable; NK, not known; PNFA, progressive nonfluent aphasia; R, right.

Case III-9

A 58-year-old right-handed woman presented with a 6-month history of increasing difficulty with the use of her hands: she became unable to dress herself, to switch on the television, and to put on spectacles. She also lost the ability to write, had problems with calculation, and her speech output became effortful, with a stammer and increasing difficulty in finding words. Over the same period, she became mildly apathetic and developed a sweet tooth. Her MMSE score was 15/30, with evidence of anomia. Neurologic examination revealed marked bilateral ideomotor and ideational limb apraxia and a predominantly left-sided asymmetric extrapyramidal syndrome, with tremor, rigidity, and myoclonus. The tendon reflexes were symmetrically brisk, with flexor plantar responses. Eye movements were abnormal, with hypometric saccades and jerky pursuit. The clinical diagnosis was FTLD with features of both CBD syndrome and nonfluent aphasia. The patient's condition deteriorated over the next 2 years, and she became immobile, mute, unable to swallow, and doubly incontinent. She died at the age of 63 years.

Case III-11

A 67-year-old right-handed woman presented with word-finding difficulty. Six months after symptom onset, her MMSE score was 28/30, with evidence of anomia. The findings of her cognitive and neurologic examination were otherwise normal. When she was assessed 1 year later, her anomia had progressed and she had developed phonemic paraphasias, agrammatism, and difficulty in repeating polysyllabic words. Her family reported that she had become apathetic and socially withdrawn. Her MMSE score had decreased to 22/30. Neurologic examination revealed no abnormalities except for mild bilateral ideomotor and ideational limb apraxia. The clinical diagnosis was PNFA.

SUMMARY OF CLINICAL FEATURES

The clinical features in this series fall within the wide phenotypic spectrum described previously for sporadic and familial FTLD.[1,11] Considering the affected individuals as a group (**Table 1**), the most consistent features are im-

Table 2. Summary of Neuropsychologic Findings at Presentation

Variable	Case III-2	Case III-4	Case III-9	Case III-11
Duration since symptom onset, y	2	2	1	1
General intellectual function				
Verbal IQ	84 ($\geq$ 10th percentile)	61 ($<$ 1st percentile)	72 (1st to $<$ 5th percentile)	85 ($\geq$ 10th percentile)
Performance IQ	72 (1st to $<$ 5th percentile)	$<$54 ($<$ 1st percentile)	60 ($<$ 1st percentile)	108 ($\geq$ 10th percentile)
Memory				
Verbal memory[a]	32/50 (1st to $<$ 5th percentile)	Fail	21/25 ($\geq$ 10th percentile)	38/50 ($\geq$ 10th percentile)
Visual memory[b]	29/50 ($<$1st percentile)	Fail	14/25 ($<$ 1st percentile)	44/50 ($\geq$ 10th percentile)
Language				
Naming[c]	16/30 ($\geq$ 10th percentile)	13/30 (5th to $<$ 10th percentile)	8/30 ($<$ 1st percentile)	3/30 ($<$ 1st percentile)
Word comprehension[d]	36/50 ($\geq$ 10th percentile)	NT	NT	33/50 ($\geq$ 10th percentile)
Word repetition	Normal	Normal	Impaired	Impaired
Other cognitive domains				
Spelling[e]	14/30 ($\geq$ 10th percentile)	NT	2/30 ($<$ 1st percentile)	17/30 ($\geq$ 10th percentile)
Calculation[f]	1/24 ($<$ 1st percentile)	0/24 ($<$ 1st percentile)	0/24 ($<$ 1st percentile)	14/24 ($\geq$ 10th percentile)
Visuospatial/perceptual skills[g]	$<$ 5th percentile	25th-50th percentile	$<$ 5th percentile	75th-90th percentile
Limb praxis	Mild impairment	Severe impairment	Severe impairment	Mild impairment
Executive function[h,i]	Fail	Fail	Fail	Normal

Abbreviation: NT, not tested.
[a] Recognition Memory Test for Words (out of 50)[14] (short version [out of 25]).
[b] Recognition Memory Test for Faces (out of 50)[14] (short version [out of 25]).
[c] Graded Naming Test.[15]
[d] Warrington Synonyms Test (out of 50).[16]
[e] Graded Difficulty Spelling Test.[17]
[f] Graded Difficulty Arithmetic Test (out of 24).[18]
[g] Visual Object and Spatial Perception battery.[19]
[h] Weigl test.[20]
[i] Modified card sorting test.[21]

paired language output, a behavioral syndrome with early and prominent apathy, and limb apraxia. Language impairment consisted of nonfluent aphasia in some cases (III-9 and III-11) and reduced quantity of spontaneous speech in others (III-2, III-3, and III-4). Parkinsonian and other extrapyramidal features emerged in 3 of the cases. None of the patients had bulbar or limb features suggestive of motor neuron disease. Hypersomnia, an infrequent feature in most FTLD series,[12,13] was prominent in 2 cases.

NEUROPSYCHOLOGIC FINDINGS

Four patients were assessed at their initial presentation (**Table 2**). Both episodic memory and executive function were impaired in patients III-2, III-4, and III-9. Patient III-11 scored within the normal range for memory but showed deterioration in recognition memory for words from above the 50th percentile at diagnosis to between the 10th and 25th percentile 1 year later and subsequently developed reduced verbal fluency. Naming was relatively preserved in patients III-2 and III-4 but was impaired in patients III-9 and III-11.[15] The latter 2 patients also had impaired word repetition, consistent with nonfluent aphasia. Simple calculation was impaired in 3 patients (III-2, III-4, and III-9), and perceptual and spatial skills were impaired in 2 patients (III-2 and III-9).

The neuropsychometric profile of these cases, taken together, is noteworthy for the relatively early involvement of parietal lobe (calculation, visuoperceptual, and visuospatial) functions. In contrast to features such as executive dysfunction, anomia, and memory impairment, which are observed in a broad spectrum of FTLD cases, including familial cases with mutations in the tau gene,[22] parietal lobe features are unusual in FTLD. Coupled with the high frequency of limb apraxia, this pattern argues for a more posterior extension of disease associated with this *PGRN* mutation than would be regarded as typical in FTLD.
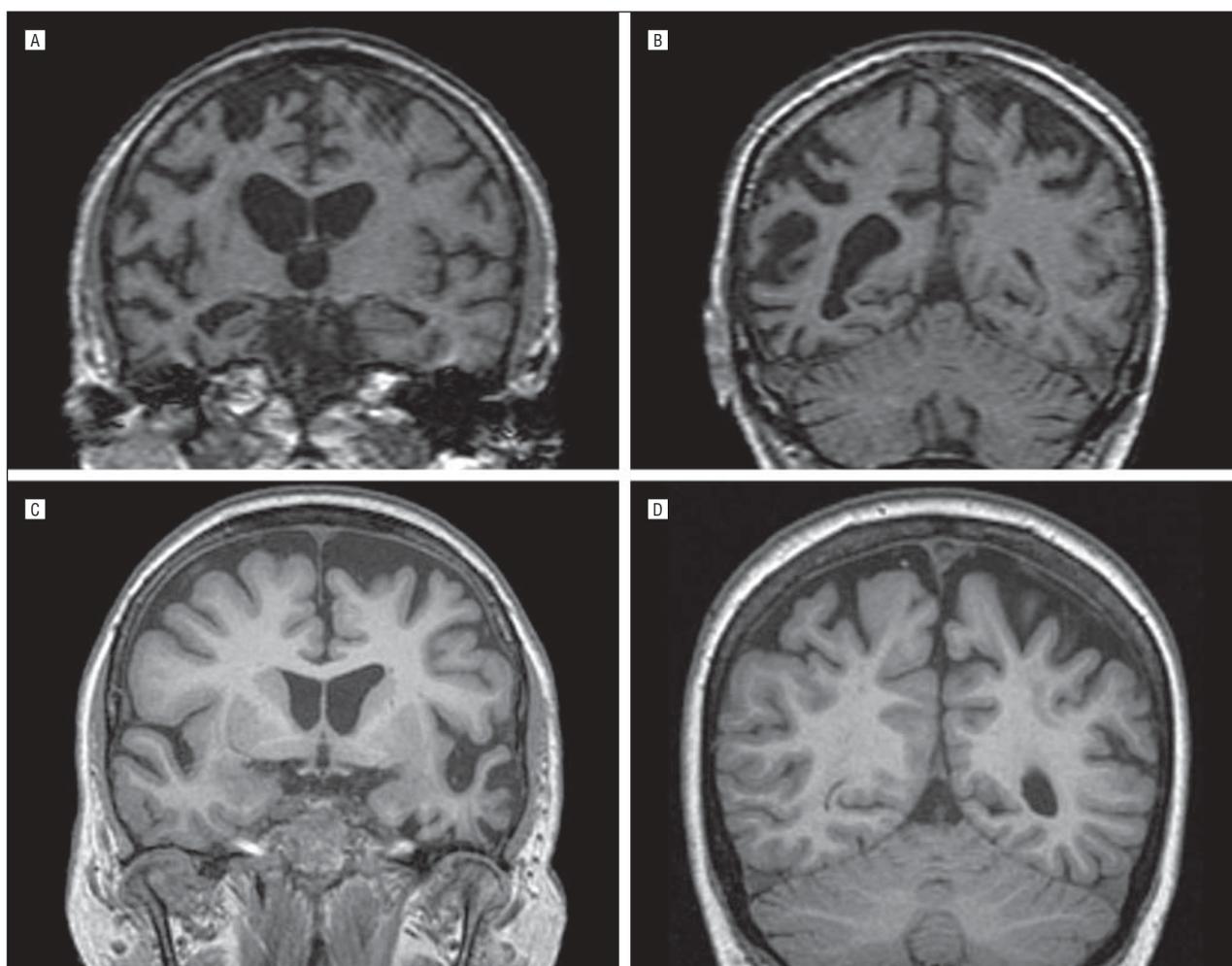
BRAIN IMAGING FINDINGS

Brain imaging was performed in 4 cases (III-2, III-4, III-9, and III-11). The findings are summarized in **Table 3**, and representative magnetic resonance images are presented in **Figure 2**. Brain imaging findings show considerable individual variation in this series, but atrophy involving the frontal, temporal, and parietal lobes was present in all cases. Cerebral atrophy was strikingly asymmetric in patients III-2 and III-4 (both predominantly right-sided) and in patient III-11 (predominantly left-sided).

NEUROPATHOLOGIC FINDINGS

Postmortem examination revealed similar findings in 3 members of the kindred (patients III-2, III-3, and III-4). Macroscopically, all 3 patients showed severe bilateral atrophy of the frontal and temporal lobes, with moderate atrophy of the parietal lobes and relative sparing of the occipital lobes. Histologic investigation showed superficial spongiosis, nerve cell loss, and gliosis of the frontal, temporal, and parietal cortices. There were numerous ubiquitin-positive neurites and neuronal cytoplasmic inclusions in the superficial cortical laminae and striatum. Scattered ubiquitin-positive, lentiform or round neuronal intra-

Table 3. Summary of Brain Imaging Findings

Case No.	Duration Since Symptom Onset, y	Modality	Key Findings
III-2	2	Magnetic resonance imaging	Marked asymmetrical frontal, temporal, and parietal lobe atrophy predominantly affecting the right side. In the frontal lobes, there is greater atrophy affecting the inferior frontal regions than the frontal convexities, although the convexity sulci are wider bilaterally. There is asymmetric temporal lobe atrophy, with the whole right temporal lobe affected more than the left. There is also widespread right-sided parietal atrophy.
III-4	1	Computed tomography	Asymmetric generalized atrophy, affecting the right hemisphere more than the left.
III-9	1	Magnetic resonance imaging	Mild diffuse atrophy with increased prominence of the parietal sulci.
III-11	1	Magnetic resonance imaging	Asymmetrical frontal, temporal, and parietal lobe atrophy predominantly affecting the left side. In the frontal lobes. there is evidence of atrophy of the medial superior frontal and frontopolar regions and involvement of the anterior cingulate gyrus. There is marked atrophy of the left temporal pole. The left superior temporal, middle, and inferior temporal and fusiform gyri are significantly affected, with some atrophy of the left amygdala and hippocampus. In the parietal lobes, there is relatively selective atrophy of the left angular gyrus posteriorly.

Figure 2. Representative brain images in 2 affected individuals (cases III-2 [A and B] and III-11 [C and D]).

nuclear inclusions were found. The dentate fascia granule cells also contained scattered neuronal cytoplasmic inclusions, which often had a granular appearance, as well as occasional neuronal intranuclear inclusions. **Figure 3** shows the findings in case III-2. All 3 cases showed features of type 3 FTLD-U according to recently revised consensus criteria,[23] which corresponds to previously reported cases with *PGRN* mutations.[24] Of note, the neurites, neuronal cytoplasmic inclusions, and neuronal intranuclear inclusions also stained for TDP-43, which has recently been described as a component of the ubiquitin-positive neurites and inclusions in FTLD-U.[25]
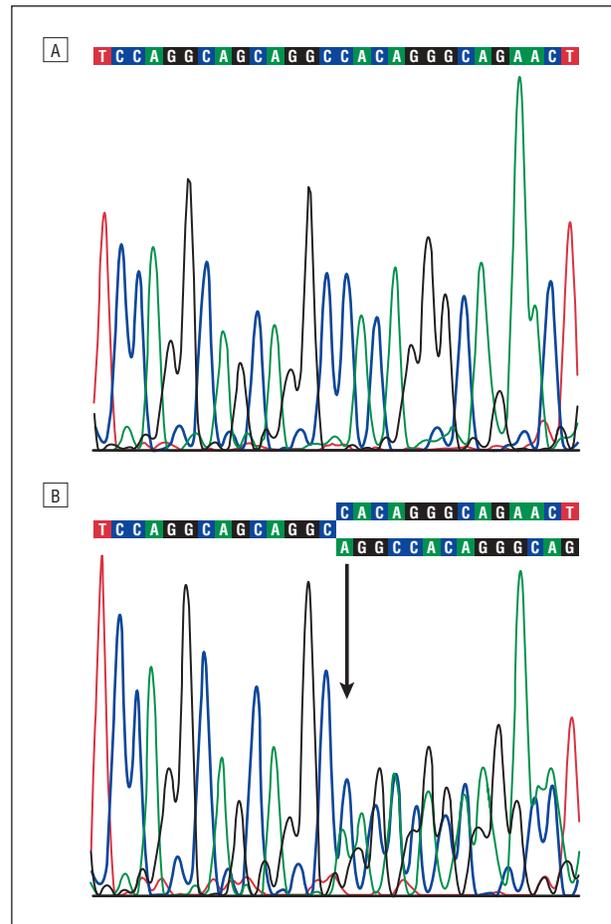
GENETIC ANALYSES

All 13 exons of the *PGRN* gene were sequenced in cases III-3 and III-11 in at least 1 direction. Analysis of the electropherogram traces revealed a c.90_91insCTGC mutation in the first coding exon on the reverse complement strand in both cases (**Figure 4** shows the electropherogram for case III-3), which would be predicted to cause a frameshift and premature termination (C31LfsX35). This mutation was originally described in the UBC17 family.[7,26] Analysis of 4 microsatellites near to *PGRN* in case III-3 identified rare alleles linked to the UBC17 mutation,[25] suggesting a common ancestry.

COMMENT

We describe the phenotype of a large family with autosomal dominant TDP-43–positive FTLD-U due to a *PGRN* mutation. Common clinical features include language output impairment leading to mutism, behavioral disturbance with early prominent apathy, and extrapyramidal features. In addition to these features, which are commonly associated with FTLD, we suggest that parietal deficits (dyscalculia, visuospatial/perceptual dysfunction, and/or limb apraxia), which are infrequently described in FTLD, may also be a feature of the progranulin phenotype. Our patient III-9 was diagnosed as having CBD syndrome, in which parietal dysfunction is well recognized[27] and which is pathologically heterogeneous.[28] Indeed, CBD syndrome has been described previously in association with a *PGRN* mutation.[9] However, it is notable that all of our patients had evidence of parietal dysfunction. Neuropsychometry may expose parietal lobe deficits that might otherwise be overlooked.

We suggest that language and behavioral features may have greater value in differentiating these cases from other causes of FTLD when accompanied by parietal deficits. Furthermore, the specific features of the speech or behavioral syndrome may also have diagnostic potential. All 5 of the patients described in detail in family DRC255 had impairment of language output. Patients III-9 and III-11 had features consistent with PNFA.[1] In contrast, patients III-2, III-3, and III-4 exhibited a decrease in the quantity of spontaneous speech in the absence of semantic, grammatical, or phonemic errors and with relatively intact naming and verbal comprehension, ie, the features of a dynamic aphasia,[29] rather than the PNFA or semantic dementia subtypes of FTLD.[1] Our cases suggest that the common end point for both the PNFA and the dynamic aphasia presentations is mutism. Behavioral features were early and prominent in cases III-2, III-3, and III-4 and less prominent in the other 2 cases. However, apathy developed as the earliest and most salient behavioral feature in all cases.
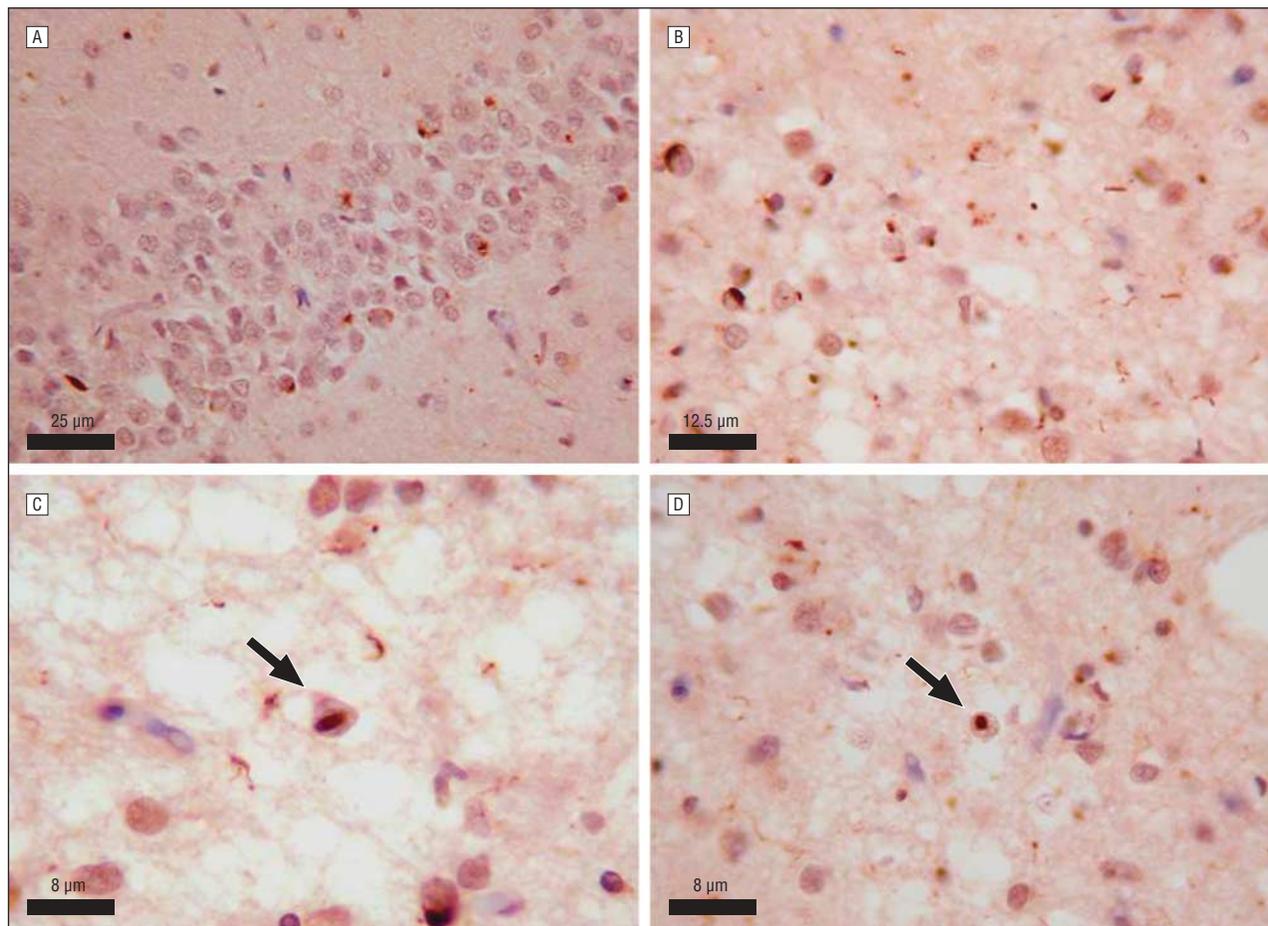
How does our family (DRC255) compare clinically with previously described families with *PGRN* mutations (1083,[30] DR2-DR8 Belgian founder family,[31] HDDD2,[32,33] HFTD3,[34,35] F53 and F337,[36] and UBC17, which appears to be the same family as DRC255[25]) and with other genetically mediated causes of FTLD, notably mutations in the tau gene? The most commonly de-

Figure 3. Electropherogram traces from the first coding exon of *PGRN* in the reverse complement. A, Healthy control DNA. B, Case III-3. The arrow indicates the presence of a c.90_91insCTGC mutation.

scribed features in patients with *PGRN* mutations are language-output impairment, with features suggestive of either dynamic aphasia or nonfluent aphasia, and a behavioral syndrome that is often characterized by apathy. Published data on the clinical phenomenologic features of patients with *PGRN* mutations are limited; however, parietal lobe features have been described in many families.[26,32,34,36] These clinical observations are further supported by histopathologic evidence of significant parietal lobe involvement in association with *PGRN* mutations.[26,32,33,36] Tau mutations are associated with wide phenotypic variation in published series.[37,38] However, in detailed studies of patients with a tau 10 + 16 mutation,[22] disinhibition rather than apathy dominated the behavioral syndrome, and while "language deficits" occurred in these patients, features of a nonfluent aphasia were not reported and language impairment was not a prominent feature. Of particular note is that parietal features are generally not described. Parkinsonism and other extrapyramidal features commonly appear to occur in association with both *PGRN* and tau mutations.[26,36-38]

The cases described in the present series showed variability in the pattern of radiologic atrophy, but it is notable that each of the cases with detailed magnetic resonance imaging showed frontotemporal atrophy with associated involvement of the parietal lobes. Longitudi-

Figure 4. Histologic features in case III-2. A, Dentate fascia ubiquitin-positive inclusions. B, Ubiquitin-positive neuronal cytoplasmic inclusions and neurites in the frontal cortex. C and D, Ubiquitin-positive neuronal intranuclear inclusions in the frontal cortex (arrows). The neuronal intranuclear inclusion in C is of the lentiform type.

nal structural imaging in 1 patient with a *PGRN* mutation revealed progressive asymmetric frontotemporoparietal atrophy that was more marked on the right side,[39] while a recent study that specifically compared *PGRN* cases with ubiquitin-positive, *PGRN*-negative cases showed that *PGRN*-positive cases had greater gray matter loss in the parietal lobes (as well as the frontal lobes).[40] Those findings, combined with the results of our study, support the hypothesis that more posterior extension of atrophy to involve the parietal lobes may be a radiologic marker for *PGRN*-associated disease, consistent with the clinical and neuropsychologic profile. The involvement of the parietal lobe as well as more anterior areas suggests that *PGRN* mutations may disrupt functional pathways linking the frontal and parietal lobes, for which anatomical substrates exist in the human brain.[41] Preferential disease spread within hemispheric pathways (rather than between hemispheres) would also be in keeping with the striking asymmetry seen early in the disease both in our own cases and in other cases reported in the literature.

In conclusion, the mutation in the *PGRN* gene in the family described in our study produces a clinicoradiologic phenotype that overlaps substantially with the spectrum of FTLD caused by other sporadic and genetically mediated pathologic processes. However, certain clinical and radiologic features that are common to a majority of affected individuals suggest that there may be a core phenotype of progranulin-associated disease. In particular, parietal lobe deficits are a salient feature of the progranulin phenotype. Future work will be directed toward testing these observations in other affected families, assessing their specificity and predictive value, and elucidating the mechanisms by which *PGRN* mutations produce their phenotypic effects.

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Author Contributions: Dr Rossor 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:* Rohrer, Warren, Omar, Mead, Pickering-Brown, and Rossor. *Acquisition of data:* Rohrer, Warren, Omar, Revesz, Holton, Pickering-Brown, and Fox. *Analysis and interpretation of data:* Rohrer, Warren, Omar, Mead, Beck, Stevens, Al-Sarraj, Pickering-Brown, Hardy, Fox, Collinge, and Warrington. *Drafting of the manuscript*: Rohrer, Warren, Omar, Holton, and Warrington. *Critical revision of the manuscript for important intellectual content*: Rohrer, Warren, Omar, Mead,

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