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Prominent Phenotypic Variability Associated with Mutations in *Progranulin*

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Abstract

Mutations in progranulin (*PGRN)* are associated with frontotemporal dementia with or without parkinsonism. We describe the prominent phenotypic variability within and among eight kindreds evaluated at Mayo Clinic Rochester and/or Mayo Clinic Jacksonville in whom mutations in *PGRN* were found. All available clinical, genetic, neuroimaging and neuropathologic data was reviewed. Age of onset ranged from 49 to 88 years and disease duration ranged from 1 to 14 years. Clinical diagnoses included frontotemporal dementia (FTD), primary progressive aphasia, FTD with parkinsonism, parkinsonism, corticobasal syndrome, Alzheimer's disease, amnestic mild cognitive impairment, and others. One kindred exhibited maximal right cerebral hemispheric atrophy in all four affected individuals, while another had maximal left hemisphere involvement in all three of the affected. Neuropathologic examination of 13 subjects revealed frontotemporal lobar degeneration with ubiquitin-positive inclusions plus neuronal intranuclear inclusions in all cases. Age of onset, clinical phenotypes and MRI findings associated with most *PGRN* mutations varied

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significantly both within and among kindreds. Some kindreds with *PGRN* mutations exhibited lateralized topography of degeneration across all affected individuals.

Keywords

Frontotemporal dementia; FTDP-17; Progranulin; PGRN; MRI

1. Introduction

In 1892, Arnold Pick first described behavioral and language abnormalities in association with frontotemporal lobar degeneration. Subsequently, many familial cases of frontotemporal dementia with parkinsonism were linked to chromosome 17 (FTDP-17) (Foster et al. 1997). Some were associated with mutations in the microtubule associated protein tau (*MAPT*),(Hutton et al. 1998; Ingram and Spillantini 2002) while others were not (Kertesz et al. 2000; Rademakers et al. 2002; Mackenzie et al. 2006b). Many cases of FTDP-17 did not exhibit immunostaining for tau on pathologic examination (Kertesz et al. 2000; Rosso et al. 2001; Savioz et al. 2003; Mackenzie et al. 2006b; van der Zee et al. 2006), and mutations in *MAPT* were absent in all of these. We recently reported several FTDP-17 kindreds having frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) neuropathology in association with mutations in the gene encoding *Progranulin* (*PGRN*) (Baker et al. 2006; Boeve et al. 2006; Gass et al. 2006; Mackenzie et al. 2006b). The eight families described here extend the phenotypic and MRI findings associated with mutations in *PGRN* and highlight the variability in presentation, clinical course and neuroimaging findings within and among kindreds.

2. Methods

2.1 Subjects

Mutations in *PGRN* were identified in eight families whose probands were evaluated at Mayo Clinic Rochester (n=6) or Mayo Clinic Jacksonville (n=2). At least one affected individual from each family was enrolled in the Mayo Clinic Alzheimer Disease Research Center, a Mayo Foundation Institutional Review Board-approved program. All available clinical records and neuroimaging studies on affected members of these kindreds were reviewed. Genetic analyses, MRI scans, and autopsies were performed after subjects or appropriate proxies provided written consent.

2.2 Clinical Evaluations

Age of onset was the age at which the subject first demonstrated behavioral or personality change, memory loss, motor changes, or other neurological changes as noted by themselves, family, friends or colleagues. All neurobehavioral clinical data (Members of the Department of Neurology 1998) were reviewed.

2.3 Laboratory Analyses

DNA was extracted from peripheral blood leucocytes and sequence analysis of *MAPT* and *PGRN* from patient genomic DNA was performed as previously described (Hutton et al. 1998; Baker et al. 2006).

2.4 Neuroimaging Examinations

MRI was performed using a GE scanner at 1.5 Tesla, and images of the brain were obtained in the sagittal (T1-weighted), axial [proton-density, T2-weighted, and fluid attenuation inversion recovery (FLAIR)], and coronal (T1-weighted and FLAIR) planes.

2.5 Neuropathologic Examination

Sections of neocortex, hippocampus, thalamus, basal ganglia, midbrain, pons, medulla and cerebellum were stained with hematoxylin and eosin and thioflavin-S fluorescent microscopy and immunocytochemistry for phospho-tau. Sections of cortex and hippocampus were stained with Bielschowsky and Luxol fast blue, and immunostained for ubiquitin, neurofilament, Aβ40, and Aβ42. Midbrain and amygdale sections were studied with alpha-synuclein immunostains. Immunohistochemistry for TDP-43 was applied in selected cases (1:8000; Proteintech Group, Chicago, IL).

Neuropathological diagnoses were based on established guidelines (McKhann et al. 2001). A diagnosis of frontotemporal lobar degeneration with ubiquitin-only immunoreactive neuronal changes (FTLD-U) was made if there was neuronal loss and gliosis affecting frontal or temporal lobe, plus ubiquitin-positive; tau, alpha-synuclein and neurofilament negative intraneuronal inclusions or neurites in frontal or temporal neocortex or hippocampal dentate granule cells in the absence of any evidence of motor neuron degeneration (Josephs et al. 2006a). In cases with multiple pathologies, TDP-43 immunohistochemistry was used to confirm FTLD-U.

3. Results

3.1 Family Descriptions

Pedigrees are shown in Figure 1. Clinical, radiologic, and neuropathologic findings are summarized in Table 1, with additional clinical details presented in Table 2. Representative MRI scans are shown in Figure 2, and Figure 3 is a schematic drawing localizing the mutations in *PGRN*. Descriptions of Kindred 7 (Mesulam et al. 2007), two members of Kindred 1 (Boeve et al. 2002) and the proband of Kindred 5 (Boeve et al. 2006) have previously been reported.

3.2 Demographics

Symptom onset among 38 individuals ranged from 49 to 88 (mean 64.5 ± 9.6 years). Of 44 individuals reported to be affected, 25 were female. Among the 18 subjects (7 male) with clinical evaluations, age at onset ranged from 49 to 80 years (mean 61.1 ± 8.1 years). In Kindred 2, mean age of symptomatic onset was 75.8 ± 5.0 years in generation II and 60.7 ± 5.5 years in generation III. In Kindred 3, mean age of symptomatic onset was 70.9 ± 10.4 years in generation III and 52 ± 2.8 years in generations IV and V.

Disease duration ranged from 1 year to 14 years, with a mean of 6.6 ± 3.2 years (31 individuals). Two individuals had accidental deaths within 1 year of onset. Excluding these, the range was 2 to 14 years (mean 7.0 ± 3.0 years). Among the 13 subjects clinically evaluated who subsequently died, mean duration was 7.15 ± 2.9 years (range 2 to 13 years).

3.3 Clinical Features

As Table 2 indicates, personality change was an initial or early symptom (developing within one year of onset) in 10 of the 18 patients evaluated clinically (55%), and later developed in another 7 patients (cumulative 94%). Hyperoral behaviors developed in 8 of the 12 patients from whom this history was collected. Executive dysfunction (evidenced on

neuropsychological testing) was an initial or early feature in 7 of 18 patients for whom this data was available (39%). It later developed in all but one of these patients (94.1%). Eleven of the 18 patients evaluated clinically (61%) had personality changes and/or executive dysfunction features within the first year of symptomatic disease. Initial memory impairment was present in 8 of the 18 patients seen clinically (44%), developing prior to personality change or executive dysfunction in 2 unrelated patients. Memory impairment was prominent enough in six members of Kindred 2 that their initial diagnoses were AD or amnestic MCI, and AD remained the final diagnosis in four individuals. Language impairment eventually developed in 16 of the 18 individuals for whom this data was available, and was an initial or early symptom in 8 (44%).

Parkinsonism was seen in 11 of 18 patients (61%). It was an initial or early symptom/sign in 3 patients (17%). In three patients, parkinsonism developed four or more years after onset.

No patient exhibited features of motor neuron disease.

3.4 Neuroimaging Findings

MRI was available for review in 14 patients and brief descriptions of the MRI findings in these kindreds are presented in Table 3. Representative images highlighting the variable patterns of atrophy and the prominent subcortical white matter FLAIR hyperintensities are presented in Figure 2. Atrophy was identified in all patients, with frontotemporal predominance in 13. Parietal cortical atrophy was present in four. Subcortical white matter signal changes with a frontal predominance were identified in six individuals, and in four subjects (cases II.4 and III.2 of Kindred 2, case V.1 of Kindred 3, and case III.1 of Kindred 5), striking signal changes were present. These subcortical signal changes were most prominent in the regions of maximal cortical atrophy, and the extent of signal change increased with disease duration (Boeve et al. 2006). In two cases with focal temporal lobe atrophy (Kindred 1 case II.1 and Kindred 2 case III.3), milder subcortical signal changes were present. Longitudinal MRI scans spanning two or more years were available in six patients, which all showed progression of atrophy, ventricular, and subcortical white matter signal changes.

In Kindred 2, the topography of cortical atrophy was variable. Kindred 1 showed right cerebral hemisphere predominance in the three affected siblings, and the same can be presumed given their father’s left-sided motor features. The opposite was apparent in Kindred 7, with all three siblings having left cerebral hemisphere atrophy.

3.5 Genetic Findings

As shown in Figure 3, a different *PGRN* mutation was identified in each family. (Baker et al. 2006; Gass et al. 2006). The specific mutations are listed in Table 1, indicating which individuals were genetically tested. Mutations in Kindreds 1, 2, 3, 6 and 7 cause frameshifts which create a premature stop codon, resulting in a null allele through nonsense-mediated decay. Similarly, the nonsense mutation in Kindred 3 induces nonsense-mediated decay. The mutation in family Kindred 5 destroys the 5′ splice site of exon 1 thereby removing the start methionine codon, completely blocking PGRN protein from being generated (Boeve et al. 2006; Gass et al. 2006). Kindred 8 carried a mutation that disrupts the signal peptide sequence. RT-PCR transcript analyses for this mutation showed strongly reduced levels of mutant RNA, confirming the generation of a null allele (Gass et al. 2006).

At least one mutation carrier remains asymptomatic more than 15 years past the age of onset of their affected siblings.

3.6 Neuropathological Findings

Neuropathological data was available for 13 affected individuals; all exhibited FTLD-U with NII. Two cases had additional pathologies present; Kindred 2 case II.1 had coexistent Alzheimer pathology with moderate to frequent neuritic plaques (NIA-Reagan high likelihood) and Braak stage V neurofibrillary tangle distribution (The National Institute on Aging 1997) as well as vascular pathology, and Kindred 4 case II.1 had coexistent diffuse Lewy body pathology (McKeith et al. 2005). Prominent areas of hyperintensity on FLAIR imaging were noted in two individuals who had tissue available for review. Representative photomicrographs of these regions are shown in Figure 4, demonstrating marked microglial activation throughout the white matter as well as myelin loss and gliosis.

4. Discussion

4.1 Clinical Considerations

Our data suggest a wide spectrum of cognitive, behavioral, and motor features in FTDP-17 associated with mutations in *PGRN*. Clinical findings characteristic of FTDP-17 - cognitive impairment (executive dysfunction and/or aphasia), behavioral changes and parkinsonism – comprise the core phenotypic features, but specific clinical and radiologic features varied widely. Prominent early memory impairment –typical of amnestic MCI and Alzheimer's disease (and an exclusionary criterion for the diagnosis of FTD) (Neary et al. 1998) – was present in several cases. Further, personality change was an early finding in only about half of the clinically evaluated patients, and was a late or absent finding in three. Levodopa-responsive parkinsonism was present in some affected individuals. A few had both visual hallucinations and parkinsonism, suggestive of Lewy body disease (McKeith et al. 2005). Some had progressive asymmetric rigidity and apraxia characteristic of the corticobasal syndrome (Boeve et al. 2003). These findings extend the range of phenotypes beyond those of previously published kindreds having *PGRN* mutations (Cruts et al. 2006; Huey et al. 2006; Masellis et al. 2006; Mukherjee et al. 2006; Snowden et al. 2006; Mesulam et al. 2007; Spina et al. 2007).

Phenotypic heterogeneity also exists within kindreds. To underscore this point, Kindred 2 had several members with primarily amnestic difficulties, one individual with PPA, another with FTDP, and one individual presented with amnestic complaints which quickly evolved into FTD. Phenotypic heterogeneity has been seen both within families and among families having identical mutations in *MAPT* as well (Bird et al. 1999).

Initial amnestic complaints occurred more frequently than would be expected in frontotemporal lobar degeneration. The proband of Kindred 5 presented with initial memory impairment suggestive of AD. Four members of Kindred 2 presented with amnestic complaints, following a course typical of AD. Another member of Kindred 2 presented with memory impairment, later following a course resembling FTD. Visuospatial deficits accompanied attention/executive impairment in three individuals clinically diagnosed with FTD. This pattern is also uncommon in FTD, but has been previously reported in a case associated with FTLD-U pathology (Meiner et al. 2005).

One sibling in Kindred 1 followed a clinical course resembling corticobasal syndrome (CBS), as did his father. His brother exhibited hemiparkinsonism late in his course, as did his sister. It has been proposed that frontotemporal lobar degeneration, CBS and progressive supranuclear palsy (PSP) represent different points of a disease spectrum on the basis of overlapping neuropathologic findings (Josephs et al. 2006b), and clinical characterization in another clinicopathologic series depended upon when in the course the subjects were evaluated (Kertesz et al. 2005). Families harboring both FTD and CBS phenotypes in association with *MAPT* mutations have been reported (Bugiani et al. 1999; Baba et al. 2007).

Others have reported families having FTD and CBS phenotypes associated with FTLD-U pathology,(Brown et al. 1998) but this report predates the association of mutations in *PGRN* with FTLD-U. Recently, familial CBS was associated with the c.708+1G>A splice donor site mutation in *PGRN* (Masellis et al. 2006) as well as a deletion in exon 7 (Benussi et al. 2006).

Parkinsonism was the predominant phenotype in Kindred 4, and CBS-like findings were present in many members of Kindred 1. Similar clinical features were seen in two other kindreds (Benussi et al. 2006; Masellis et al. 2006). It is unclear whether parkinsonism is more predominant in association with certain *PGRN* mutations, analogous to the parkinsonian predominant phenotype associated with the N279K mutation in *MAPT*. Presumably, this reflects more prominent extrapyramidal system pathology, but how specific mutations may direct the topography of pathology is not known. Two previous *PGRN* case-control studies reported higher frequencies of parkinsonism than this series (Josephs et al. 2007; Whitwell et al. 2007). Those series studied autopsy-confirmed cases associated with *PGRN* mutations, and the lower frequency in this series may reflect that some subjects of this study are still living and may later develop parkinsonism.

The apparent hemispheric predilection in some kindreds raises similar questions. The right cerebral hemisphere was maximally affected in four members of Kindred 1, and the left hemisphere was maximally affected in our Kindred 7, as well as the PPA3 and HDDD2 kindreds (Mukherjee et al. 2006; Mesulam et al. 2007). This hemispheric predilection has not been described in kindreds with mutations in *MAPT*. As previously suggested (Boeve et al. 2002), some genetic factors may dictate the development of neurologic disease, while others may determine the neurodegenerative topography, analogous to prion disease (Goldfarb et al. 1992).

No case had motor neuron disease (MND), and only one report has suggested the involvement of *PGRN* mutations in the development of ALS (Spina et al. 2007). In that case, a FTD patient with a strong family history of ALS was found to have a *PGRN* missense mutation (R433W). This individual had clinical manifestations suggestive of motor neuron disease as well. Neuropathologic examination identified FTLD-U, but without NII as well as pathological changes suggestive of motor neuron disease. The relationship between this family's ALS and the *PGRN* mutation is not entirely clear. These data suggest that in contrast to *MAPT*, MND associated with mutations in *PGRN* may be quite rare (Mackenzie et al. 2006a; Josephs et al. 2007).

Sparse detail was available regarding the first generations in most families, and some later-onset cases may represent incident AD cases. However, one individual with onset at age 79 had neuropathological FTLD-U with NII, and one mutation carrier is asymptomatic at age 73. Given the high penetrance, with 90% of subjects estimated to be symptomatic by age 70 (Gass et al. 2006), as well as the late age of onset in some individuals, it is possible that some late-onset cases had underlying FTLD-U with NII pathology.

In aggregate, age of onset varied, with some individuals presenting in their 50's and others becoming symptomatic in their 80's. This was also true within two large kindreds (Kindreds 2 and 3), although in both of these kindreds, age of onset in the earlier generation was over 10 years older than that in subsequent generations. Generations II and III of Kindred 2 were particularly well characterized, and the mean age of onset in generation III was 15 years later than that of generation II (Table 2). In comparison to familial FTD associated with mutations in *MAPT*, the mean age of onset in our kindreds was older (64.5 years versus 45 years) and the mean disease duration somewhat shorter (6.6 years versus 8.4 years) (Baba et al. 2005).

We did not identify any gender-specificity in phenotype, but limited data regarding previous generations was available. Progranulin's role in gender-specific brain development (Suzuki and Nishiahara 2002) may suggest gender-based differences in presentation and/or pattern of atrophy, warranting further study.

4.2 Neuroimaging Considerations

The MRI findings in FTD linked to charged multivesicular body protein 2B (*CHMP2B*) on chromosome 3 (Brown et al. 2004; Skibinski et al. 2005), to the valosin-containing protein (*VCP*) on chromosome 9 (Vance et al. 2006) and to *MAPT* on chromosome 17 have been frontotemporal cortical abnormalities varying from symmetric to markedly asymmetric atrophy (Basun et al. 1997; Rosso et al. 2001; Boeve et al. 2005). Most descriptions of MRI findings in sporadic and familial FTD have not reported subcortical white matter signal changes. In FTD-MND associated with chromosome 9, MRI has demonstrated "striking frontal lobe atrophy and an absence of signal change in the white matter of both hemispheres"(Vance et al. 2006). Subtle signal changes of medial temporal regions were noted in the pallidopontal nigral degeneration (PPND) kindred (Frank et al. 2007). Four of our cases with *PGRN* mutations had striking increased signal in the subcortical white matter adjacent to the cortical regions where atrophy was maximal, and in two other cases with focal temporal lobe atrophy, milder degrees of subcortical signal changes were present. Few FTDP cases with *PGRN* mutations and MRI scans have been reported, and the MR images and data presented in this report, along with our other reports (Boeve et al. 2002; Boeve et al. 2005), provide far more detail than other reports of *PGRN* mutation families. The relative sensitivity and specificity of these subcortical signal changes for cases harboring a *PGRN* mutation remains to be determined.

A recent volumetric analysis comparing individuals having FTLD-U neuropathology suggested a more severe and widespread pattern of atrophy involving the frontal, temporal and even parietal cortex in those having *PGRN* mutations (Whitwell et al. 2007) compared to those without *PGRN* mutations. Additional analyses are warranted to further investigate the neuroimaging correlates in FTLD-U with and without associated *PGRN* mutations and in the tauopathies with and without associated *MAPT* mutations.

4.3 Neuropathologic Considerations

Many cases of "dementia lacking distinctive histology" (Knopman et al. 1990) have subsequently been shown to exhibit positive immunostaining for ubiquitin (Josephs et al. 2004; Lipton et al. 2004; Mackenzie et al. 2006c). In our series, brain tissue was available in 13 cases. Neuropathologic examination in all 13 cases demonstrated features of FTLD-U with NII. The presence of NII is a feature of FTLD-U with *PGRN* mutations, but is not specific for this diagnosis as NII have been observed in FTLD-U cases without *PGRN* mutations (Josephs et al. 2007) and in FTLD due to mutations in *VCP* (Forman et al. 2006). None of our cases had pathological evidence of motor neuron disease. We confirm that FTLD-U pathology can underlie the CBS, as previously reported (Grimes et al. 1999; Benussi et al. 2006; Masellis et al. 2006).

Two cases had mixed pathologies; one had FTLD-U with Alzheimer and vascular pathology, and the other FTLD-U plus Lewy body disease. A recent study suggested that anti-TDP-43 antibodies are specific to inclusions in FTLD-U (Neumann et al. 2006), which we used to confirm the diagnosis of FTLD-U in our two cases with mixed pathologies. Therefore, we suggest that TDP-43 immunohistochemistry be considered in cases with clinical features of FTD, but pathological diagnosis other than FTLD. In two cases with striking FLAIR abnormalities, myelin loss and gliosis with associated microglial activation was demonstrated in these regions.

4.4 Disease Mechanism Considerations

All *PGRN* mutations reported in this study are expected to create functional null alleles, predominantly as a result of reading frame shifts and the creation of premature termination codons, such that no progranulin protein is expressed. This is proposed to lead to haploinsufficiency, whereby the single normal copy of the gene is incapable of producing sufficient protein to assure normal function. We suspect this lack of progranulin causes neurodegeneration, but the precise neurodegenerative mechanisms are unknown. Transgenic mouse models will soon enable investigators to test whether replacement of progranulin, or agents that increase progranulin production or secretion, can modulate neurodegeneration.

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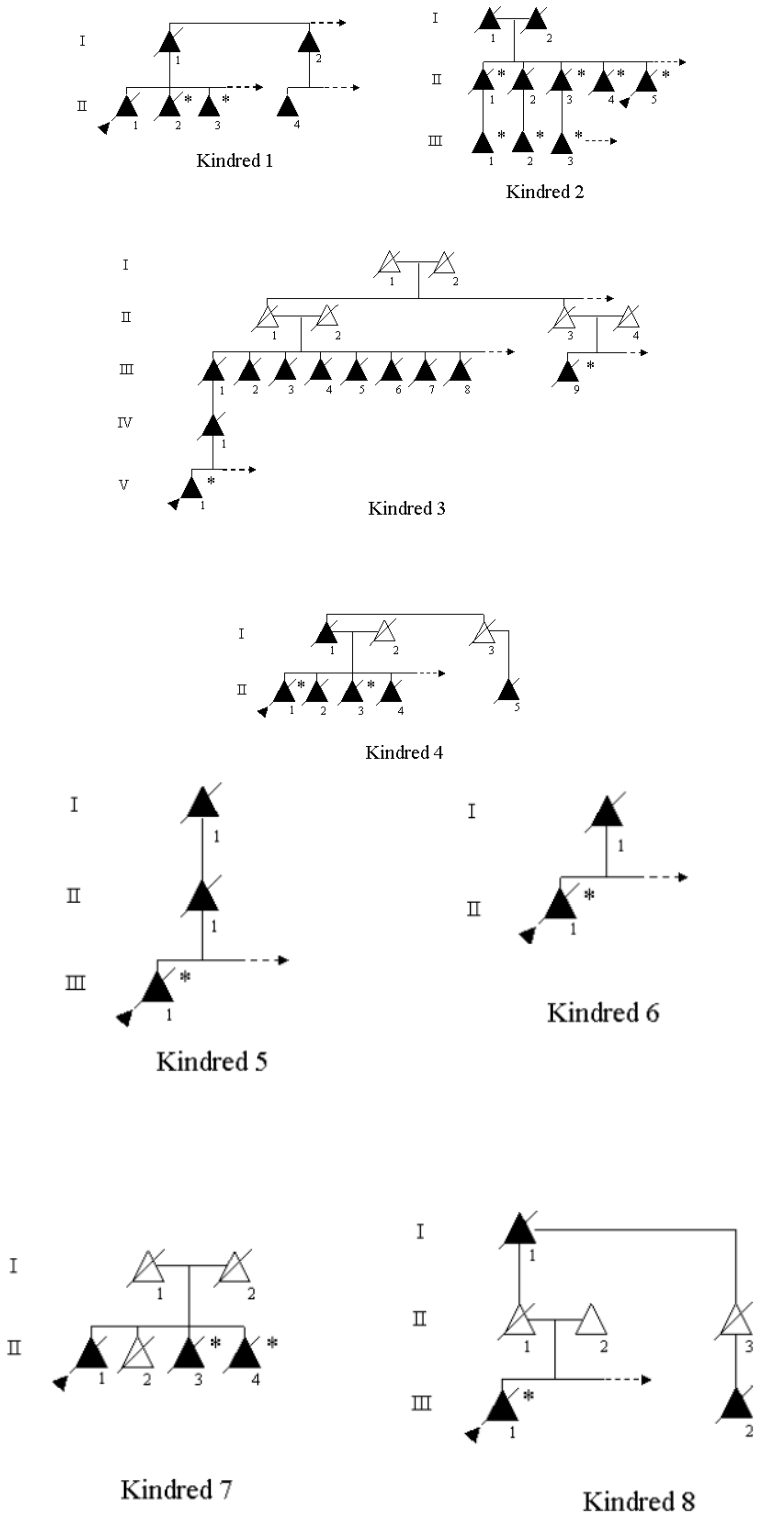

Figure 1.

Pedigrees of the eight kindreds. Triangles represent individuals, shaded triangles represent affected individuals. Triangles with diagonal lines through them represent deceased individuals. The proband is indicated by a shaded arrowhead. Individuals with a confirmed

progranulin mutation are indicated by an asterisk. An arrow pointing to the right in a sibship represents additional unaffected persons, but they were purposefully excluded to maintain confidentiality.

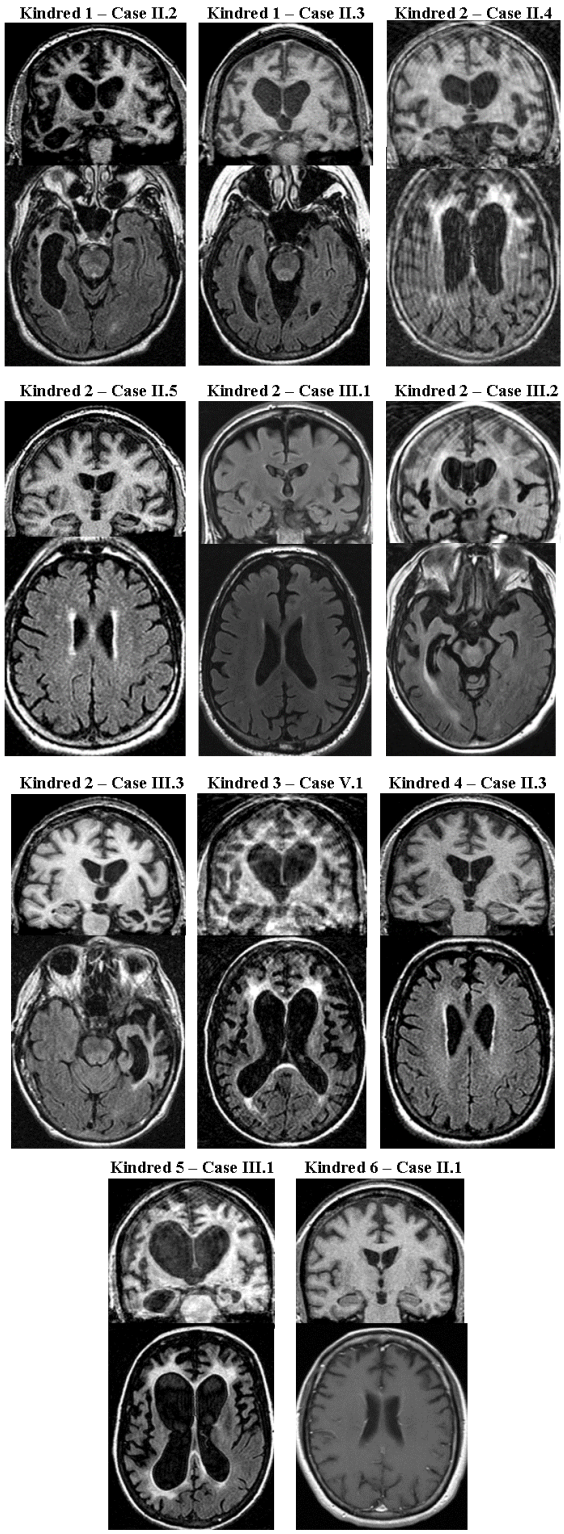

Figure 2.

Representative coronal [T1-weighted or fluid attenuation inversion recovery (FLAIR)] (top), and axial T1-weighted or FLAIR (bottom) images for each affected individual for which

MRI scans were available. Note the variability in the patterns of cerebral atrophy and degree of signal changes on FLAIR images.

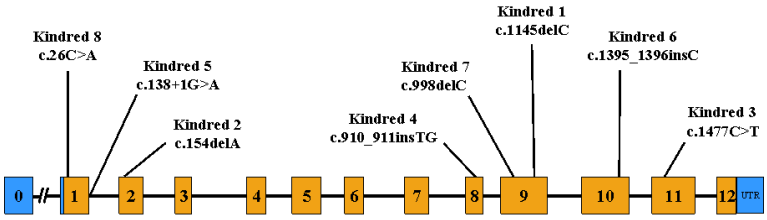

Figure 3.
Schematic representation of the progranulin (*PGRN*) gene illustrating the location of the mutations in the eight kindreds. Mutations are numbered according to GenBank Accession number NM_002087.2.

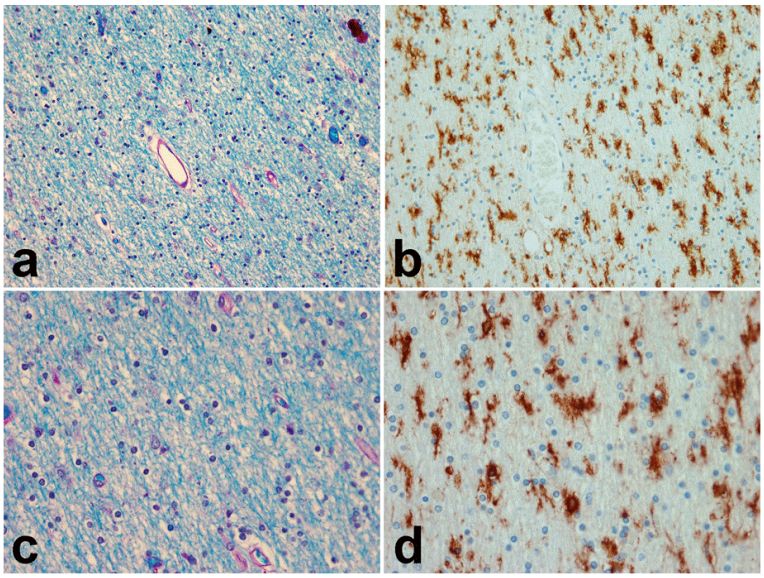

Figure 4.
Photomicrograghs showing myelin rarefaction and vacuolation, worse around blood vessels. Microglial stain (B and D) shows marked microglial activation throughout the white matter. Adjacent Luxol fast blue stain (A and C) shows myelin loss and gliosis.

Table 1

Demographic, clinical, neuropathologic, and genetic findings of all affected individuals

Kindred	Case	Duration (years)	Initial Diagnosis	Current/Final Diagnosis	Autopsy Findings	PGRN Mutation	Reference
Kindred 1	I.1	5	dementia NOS	encephalomalacia			
	I.2	*	dementia NOS	dementia NOS			
	II.1 (P)	6	PD	CBS	FTLD-U NII		Boeve et al, 2002
	II.2	7	FTD	FTDP	FTLD-U NII	c.1145delC	Boeve et al, 2002
	II.3	>4	FTD	FTD/CBS		c.1145delC	
	II.4	*	dementia NOS	dementia NOS			
Kindred 2	I.1	5	AD	AD			
	I.2	3	dementia NOS	dementia NOS			
	II.1	7	AD	AD	FTLD-U NII + AD + VD	c.154delA	
	II.2	*	dementia NOS	dementia NOS			
	II.3	2	AD	AD + Park	FTLD-U NII	c.154delA	
	II.4	7	AD	FTD	FTLD-U NII	c.154delA	
	II.5 (P)	7	amnestic MCI	AD	FTLD-U NII	c.154delA	
	III.1	>2	amnestic MCI + dep	amnestic MCI + dep		c.154delA	
	III.2	>7	FTD/DLB	FTDP		c.154delA	
	III.3	>7	PPA	PPA/FTD		c.154delA	
Kindred 3	III.1	9	dementia NOS	dementia NOS			
	III.2	7	dementia, AD	AD			
	III.3	1 (fire)	dementia NOS	dementia NOS			
	III.4	9	dementia NOS	dementia NOS			
	III.5	>2	dementia NOS	dementia NOS			

Kindred	Case	Duration (years)	Initial Diagnosis	Current/Final Diagnosis	Autopsy Findings	PGRN Mutation	Reference
	III.6	*	dementia NOS	dementia NOS			
	III.7	5	dementia NOS	dementia NOS			
	III.8	7	dementia NOS	dementia NOS			
	III.9	3	AD	AD	FTLD-U NII	c.1477C>T	
	IV.1	1 (MVA)	not Dx	not Dx			
	V.1 (P)	6	FTD	FTD		c.1477C>T	
Kindred 4	I.1	5	PD	PD			
	II.1 (P)	13	PD	PD + D	FTLD-U NII + LBD	c.910_911insTG	
	II.2	7	dementia NOS	dementia NOS			
	II.3	8	FTD	FTD	FTLD-U NII	c.910_911insTG	
	II.4	*	PD	PD + dementia NOS			
	II.5	*	PD	PD			
Kindred 5	I.1	13	dementia NOS	dementia NOS			
	II.1	7	dementia NOS	dementia NOS			
	III.1 (P)	7	AD	FTD	FTLD-U NII	c.138+1G>A	Boeve et al, 2006
Kindred 6	I.1	5	dementia NOS	dementia NOS			
	II.1 (P)	5	FTD	FTD	FTLD-U NII	c.1395_1396insC	
Kindred 7	II.1	12	PPA	PPA			Mesulam et al, 2007
	II.3	4	PPA	PPA	FTLD-U NII	c.998delG	Mesulam et al, 2007
	II.4 (P)	8	PPA	PPA	FTLD-U NII	c.998delG	Mesulam et al, 2007
Kindred 8	I.1	14	aphasia	aphasic dementia			
	III.1 (P)	>4	PPA	PPA		c.26C>A	
	III.2	*	aphasia	aphasic dementia			

Abbreviations: AD=Alzheimer's disease; CBS=corticobasal syndrome; dep=depression, DLB=dementia with Lewy bodies; FTD=frontotemporal dementia; FTDP=frontotemporal dementia and parkinsonism; FTLD-U NII=frontotemporal lobar degeneration with ubiquitin positive inclusions and neuronal intranuclear inclusions; LBD=Lewy body disease; MCI=mild cognitive impairment; MVA=motor vehicle accident; NOS=not otherwise specified; not Dx=not diagnosed; park=parkinsonism; PD=Parkinson's disease; PPA=primary progressive aphasia; VD=vascular dementia; * = unknown, (P)=proband

Table 2

Specific clinical features among affected individuals examined at Mayo Clinic

Kindred	Case	Personality Change	Hyperoral	Executive Dysfunction	Memory Dysfunction	Language Dysfunction	Parkinsonism
1	II.1	mid		mid	mid	mid	early
	II.2	early	late	mid	mid	late	mid
	II.3	early	late	early	early	absent	late
2	II.3	early			early	mid	early
	II.4	early	early	early		early	late
	II.5	mid	late	early	early	late	late
	III.1	early		early	early	absent	absent
	III.2	early	mid	early	mid	late	late
	III.3	late		late	late	early	absent
3	V.1	early	mid	later	early	early	mid
4	II.1	mid		late	mid	late	early
	II.3	early		mid	early	later	absent
5	III.1	early	mid	early	early	late	late
6	II.1	early	mid	early	early	early	absent
7	II.1	absent	absent	present	present	early	absent
	II.3	present	present	late	absent	early	mid
	II.4	present	absent	mid	absent	early	absent
8	III.1	absent	absent	absent	absent	early	absent

early=onset within first year of symptoms; mid=onset 1-2 years after symptom onset; late=onset 3 or more years after onset; absent=no evidence in clinical records of this feature being present. Empty fields reflect insufficient details in the clinical record to determine if that feature was present or absent.

Table 3

Descriptive MRI findings in affected individuals

Case	MRI Findings
Kindred 1 II.2	Asymmetric right greater than left frontotemporal atrophy, and lesser right parietal and occipital atrophy. Subcortical white matter changes were associated with this atrophy. Subsequent imaging confirmed progression of these findings.
Kindred 1 II.3	Mild temporal and hippocampal atrophy, and subtle subcortical white matter changes, greater on the right than the left
Kindred 2 II.4	Prominent frontotemporal atrophy and bilateral frontal white matter T2 hyperintensity with extension into the cortex
Kindred 2 II.5	Mild atrophy along the falx anteriorly, more obvious atrophy in the left mesial and inferolateral temporal lobe and mild leukoaraiosis
Kindred 2 III.1	Mild diffuse atrophy, more obvious along the anterior falx, without significant mesial temporal atrophy
Kindred 2 III.2	Moderately severe generalized cerebral atrophy, most prominent in the right temporal lobe. Mild subcortical white matter T2 hyperintensity evident in the right temporal lobe.
Kindred 2 III.3	Initial MRI showed marked atrophy of the left anterior temporal lobe and mild atrophy of the left frontal opercular region. Subsequent MRI examinations demonstrated progressive left hemispheric atrophy, most severely in the temporal lobe
Kindred 3 V.1	Moderately severe atrophy, most prominent in the frontal and temporal lobes. Increased T2 signal in the frontal subcortical white matter adjacent to the lateral ventricles
Kindred 4 II.3	Moderate anterior falcine atrophy without white matter signal changes
Kindred 5 III.1	Marked bilateral frontotemporoparietal atrophy particularly on the right, with subcortical white matter changes
Kindred 6 II.1	Mild diffuse cortical atrophy, slightly more prominent along the falx anteriorly
Kindred 7 II.3	Progressive left temporal atrophy with less severe frontal atrophy apparent on subsequent neuroimaging
Kindred 7 II.4	Progressive left temporal and parietal atrophy with enlargement of the Sylvian fissure
Kindred 8 III.1	Mild left frontotemporal atrophy