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Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study

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Frontotemporal dementia (FTD), characterized by behavioural and language disorders, is a clinically, genetically and pathologically heterogeneous group of diseases. The most recently identified of the four known genes is *GRN*, associated with 17q-linked FTD with ubiquitin-immunoreactive inclusions. *GRN* was analysed in 502 probands with frontal variant FTD (fvFTD), FTD with motoneuron disease (FTD-MND), primary progressive aphasia (PPA) and corticobasal degeneration syndrome (CBDS). We studied the clinical, neuropsychological and brain perfusion characteristics of mutation carriers. Eighteen mutations, seven novel were found in 24 families including 32 symptomatic mutation carriers. No copy number variation was found. The phenotypes associated with *GRN* mutations vary greatly: 20/32 (63%) carriers had fvFTD, the other (12/32, 37%) had clinical diagnoses of

PPA, CBDS, Lewy body dementia or Alzheimer's disease. Parkinsonism developed in 13/32 (41%), visual hallucinations in 8/32 (25%) and motor apraxia in 5/21 (24%). Constructional disorders were present in 10/21 (48%). Episodic memory disorders were frequent (16/18, 89%), consistent with hippocampal amnestic syndrome in 5/18 (28%). Hypoperfusion was observed in the hippocampus, parietal lobe and posterior cingulate gyrus, as well as the frontotemporal cortices. The frequency of mutations according to phenotype was 5.7% (20/352) in fvFTD, 17.9% (19/106) in familial forms, 4.4% in PPA (3/68), 3.3% in CBDS (1/30). Hallucinations, apraxia and amnestic syndrome may help differentiate *GRN* mutation carriers from others FTD patients. Variable phenotypes and neuropsychological profiles, as well as brain perfusion profiles associated with *GRN* mutations may reflect different patterns of neurodegeneration. Since all the mutations cause a progranulin haploinsufficiency, additional factors probably explain the variable clinical presentation of the disease.

Keywords: *PGRN*; *GRN*; progranulin; frontotemporal dementia; FTDU-17; primary progressive aphasia; corticobasal degeneration; ubiquitin-positive inclusions

Abbreviations: CBDS = corticobasal degeneration syndrome; FAB = frontal assessment battery; FTLD = frontotemporal lobar degenerations; FDR = False Discovery Rate; FRCT = free and cued recall test; fvFTD = frontal variant frontotemporal dementia; FTD = frontotemporal dementia; LBD = Lewy body dementia; MND = motoneuron disease; NIFID = neuronal intermediate filament inclusion disease; PNFA = progressive non-fluent aphasia; PPA = primary progressive aphasia; QMPSF = quantitative multiplex PCR of short fluorescent fragments; SD = semantic dementia

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Introduction

Frontotemporal dementia (FTD) is characterized by behavioural and language disorders, and is clinically, pathologically and genetically heterogeneous. Three variants are distinguished by the presenting symptoms and regional pattern of atrophy: frontal variant (fvFTD) with predominant behavioural disorders; semantic dementia (SD) and progressive non-fluent aphasia (PNFA), in which language disorders predominate (Neary *et al.*, 1998; Kertesz *et al.*, 1999, 2005). There are four pathological categories of frontotemporal lobar degenerations (FTLD) with either: hyperphosphorylated tau-positive aggregates (tauopathies); ubiquitin-positive, TDP-43-positive, tau- and synuclein-negative inclusions (FTLD-U); neuronal intermediate filament inclusion disease (NIFID); or no detectable inclusion (Kertesz *et al.*, 2005; Cairns *et al.*, 2007).

Mutations in *MAPT* (microtubule-associated protein tau) were initially identified in families with FTD-Parkinsonism linked to the chromosome 17 (FTDP-17), associated with tau-positive inclusions (Hutton *et al.*, 1998; Poorkaj *et al.*, 1998; Spillantini *et al.*, 1998). Recently, mutations in the progranulin gene, 1.7 Mb centromeric to *MAPT*, were found in FTD families linked to the chromosome 17 with ubiquitin-positive, tau-negative inclusions (FTDU-17) (Baker *et al.*, 2006; Cruts *et al.*, 2006). The symbol for the progranulin gene is *GRN* (HUGO nomenclature) but *PGRN* is also used. *GRN* codes for progranulin, the precursor of granulin proteins, a 593 amino acid glycoprotein containing 7.5 cysteine-rich tandem repeats. Progranulin is a secreted growth factor expressed in a variety of tissues that has been implicated in development, wound repair, inflammation and tumourigenesis (Ahmed *et al.*, 2007). It is highly expressed in neurons of the cerebral cortex, the hippocampus and in the cerebellum (Daniel *et al.*, 2000), but its function in the central nervous system is unknown. Ubiquitin-positive inclusions in FTLD-U patients with *GRN* mutations do not contain progranulin (Baker *et al.*, 2006), consistent with the fact that most *GRN* mutations are nonsense, frameshift or splice-site mutations producing mutant mRNAs with premature translation termination codons. Mutant mRNA with these codons is degraded by nonsense-mediated decay that prevents expression of truncated proteins (null mutation). As a result, no mutant protein is produced (Baker *et al.*, 2006; Cruts *et al.*, 2006). Neurodegeneration therefore results from a partial loss of progranulin function rather than the aggregation of the mutant protein. How the mutant protein causes ubiquitin-positive inclusions is unknown. However, TDP-43 (TAR-DNA binding protein) was recently identified as a major component of inclusions in FTLD-U with or without *GRN* mutations and in isolated motoneuron disease (MND) (Neumann *et al.*, 2006).

Patients with *GRN* mutations have variable ages at onset and phenotypes. FvFTD is most frequent, but primary progressive aphasia (PPA) (Snowden *et al.*, 2006; Mesulam *et al.*, 2007), hereditary dysphasic disinhibition dementia (Mukherjee *et al.*, 2006; Behrens *et al.*, 2007) or corticobasal degeneration syndrome (CBDS) (Benussi *et al.*, 2006; Masellis *et al.*, 2006) have been reported in a few families. The frequency of *GRN* mutations has not been evaluated, however, in series of patients with PPA and CBDS. A few studies on large numbers of patients have focused on genetic (Gass *et al.*, 2006) or neuropathological aspects of the disease (Davion *et al.*, 2007; Josephs *et al.*, 2007; Mackenzie, 2007). A recent study reported clinical characteristics in a series of 37 patients analysed for a single

Table 1 Characteristics of the four groups of patients analysed for *GRN* mutations

	fvFTD	FTD-MND	PPA	CBDS
Number of probands	352	52	68	30
Gender, M/F (%)	184/168 (52%/48%)	30/22 (58%/42%)	33/35 (49%/51%)	16/14 (53%/47%)
Familial/non-familial cases (%)	106/246 (30%/70%)	22/30 (42%/58%)	15/53 (22%[a]/78%)	6[a]/24 (20%[a]/80%)
Mean age at onset (y) [range]	59.4 ± 9.4 [28–79]	62.0 ± 7.9 [40–74]	63.8 ± 8.5 [48–83]	61.8 ± 9.7 [47–80]
Mean age at examination (y) [range]	63.6 ± 9.3 [30–84]	64.9 ± 7.9 [49–80]	68.5 ± 9.0 [51–87]	66.7 ± 9.8 [49–85]
Mean disease duration at examination (y) [range]	4.2 ± 2.5 [1–13]	3.0 ± 1.8 [1–9]	4.8 ± 2.4 [2–11]	4.2 ± 2.3 [1–10]
Number of probands with *GRN* mutation	20[b]	0	3	1
Frequency of mutations in probands	5.7% (20/352)	0% (0/52)	4.4% (3/68)	3.3% (1/30)

Percentages are given in brackets. [a]Family history of dementia or other FTLD disease. [b]18 probands had diagnoses of fvFTD at onset, and two probands had initial diagnoses of LBD that were subsequently changed to fvFTD.
CBDS = corticobasal degeneration syndrome; F = female; fvFTD = frontal variant of frontotemporal dementia;
FTD-MND = frontotemporal dementia associated with motoneuron disease; M = male; PPA = primary progressive aphasia; y = years.

mutation p.Arg493X (Rademakers *et al.*, 2007). However, the clinical data were collected retrospectively in this study. Neuropsychological characteristics and brain perfusion profiles associated with *GRN* mutation have not yet been described in large series of mutation carriers. We have analysed *GRN* in 502 patients including 352 patients with fvFTD, 52 with FTD and MND (FTD-MND), 68 with PPA and 30 with CBDS. We found 18 null mutations in 24 families and report clinical, neuropsychological and brain imaging features of 32 mutation carriers. Some aspects of this study, in particular the neuropsychological characteristics, as well as the brain perfusion characteristics in mutation carriers, have never been described in detail and constitute major new findings.

Methods

Recruitment of patients

Five hundred and two unrelated probands were recruited between 1997 and 2007 through a national network of 15 specialized dementia centres, 350 of which were evaluated prospectively, that is to say after inclusion in the research cohort, with standardized clinical, behavioural, neuropsychological procedures and were included in a follow-up study whenever possible (Le Ber *et al.*, 2006). The clinical evaluation included testing for: parkinsonism, other movement disorders, oculomotor abnormalities, MND, hallucinations, apraxia. The behavioural evaluation was based on a 70-item scale derived from the Frontal Behavioural scale (Lebert *et al.*, 1998), the Frontal Behavioural Inventory (Kertesz *et al.*, 2000) and the Neuropsychiatric Inventory (Cummings *et al.*, 1994), integrating apathy, disinhibition, hyperorality, stereotyped/ritualistic behaviours, emotional/affects and language. Evaluations were collected for each patient, and each symptom was evaluated during follow-up as stable, increased or decreased.

Among the 502 probands, 352 probands had fvFTD according to international clinical criteria (Neary *et al.*, 1998; The Lund and Mancheter groups, 1994), 52 FTD-MND, 68 had PPA (Neary *et al.*, 1998; Mesulam, 2001) and 30 had clinically diagnosed CBDS (Boeve *et al.*, 2003) (Table 1).

Information concerning the family was collected for each proband. Inheritance was considered autosomal dominant when at least one other patient from a different generation than the proband had a history of dementia, PPA or CBDS. The families of the probands with at least one other affected member were extended through the research network. Relatives who had neurodegenerative or neuropsychiatric disorders were examined according to the network procedure whenever possible.

In this article, we use the term proband to designate the index case of each family. Relatives are other members of proband's family, and affected relatives are family members who had dementia, PPA or CBDS. Mutation carriers are all individuals carrying *GRN* mutations (probands or relative). Phenocopies are relatives that do not carry the mutation although their phenotype is similar to that of mutation carriers. CBDS refers to the patients with clinically diagnosed corticobasal degeneration syndrome but no pathological confirmation.

Mutation screening

DNA was collected with informed consent from the 502 probands. The study was approved by the Paris-Necker ethics committee. *MAPT* mutations were excluded in fvFTD and FTD-MND patients. *GRN* comprises 13 exons that were sequenced in the 502 probands and in 179 neurologically healthy control individuals of French origin. Thirteen relatives of nine probands with *GRN* mutations were also analysed: 11 with dementia, PPA or CBDS, one with schizophrenia and one obligate carrier who was asymptomatic when sampled at age 60.

All *GRN* exons, including the non-coding exon 0, and at least 50 bp of the flanking intronic regions were sequenced in both directions. Total genomic DNA was prepared from peripheral blood according to standard procedures. Exons and flanking regions were amplified by PCR on genomic DNA (20 ng) using previously described primers (Cruts *et al.*, 2006). Amplification products were purified with 1 U Antarctic phosphatase (New England Biolabs, Ipswich, MA, USA) and 1 U exonuclease I (New England Biolabs) and sequenced in both directions using the BigDye Terminator Cycle Sequencing kit v3.1 (Applied Biosystems, Foster City, CA, USA) on an ABI3730 automated sequencer (Applied Biosystems). Sequences were analysed using Seqscape® software and the Software Package NovoSNP.

We have also looked for deletions of the *GRN* gene, which might, like most *GRN* mutations, be responsible for the partial loss of functional progranulin. Two hundred and ten patients with fvFTD or FTD-MND, in whom no mutations were detected by sequencing, were screened for *GRN* gene copy number variations

by quantitative multiplex PCR of short fluorescent fragments (QMPSF), in which multiple short genomic sequences are amplified simultaneously with dye-labelled primers under quantitative conditions (Rovelet-Lecrux *et al.*, 2006). Nine amplicons within or bordering nine exons of *GRN* were examined (details available upon request).

Phenotype of mutation carriers

Thirty-two affected patients, who carried *GRN* mutations, including 24 probands and eight affected relatives for whom sufficient clinical data was available, were included in the clinical study. All but three were examined by one of us in a memory disorders clinic. Twenty were assessed prospectively for neurological and behavioural signs using a standardized questionnaire evaluating apathy, disinhibition, emotion/affect, stereotyped/ritualistic behaviours, eating/oral behaviours, attention/executive and language disorders, and were included in a follow-up study by the research network (see the section Recruitment of patients). Clinical data were also taken from the medical records and reports by relatives. Ten index patients with mutations were previously described (Le Ber *et al.*, 2007; van der Zee *et al.*, 2007). Age at onset was when the first symptom appeared according to the principal informant and the patient.

Neuropathological examinations were performed in five mutation carriers. Ubiquitin, tau, β-amyloid and alpha-synuclein immunochemistry was performed in five patients and TDP-43 immunochemistry in four (see Supplementary data).

Neuropsychological evaluation

Twenty-two of the 32 mutation carriers were evaluated with a neuropsychological battery including evaluation of: (i) global efficiency with the mini-mental status examination (MMSE) (Folstein *et al.*, 1975) and the Mattis dementia rating scale (Mattis-DRS) (Mattis, 1988); (ii) verbal episodic memory with the free and cued recall test (FRCT), a specific procedure allowing to distinguish encoding, storage and retrieval deficits (Van der Linden *et al.*, 2004); (iii) executive functions with the frontal assessment battery (FAB) (Dubois *et al.*, 2000) and two verbal fluency tasks (Thuillard and Assal, 1991); (iv) constructional disorders with the Rey–Osterrieth's complex figure (Rey, 1959); (v) search of motor apraxia (motor programmation and bi-manual coordination), ideomotor apraxia (transitive and intransitive gesture on verbal command and imitation), ideational apraxia (use of tools) and (vi) language with tests of verbal fluency and pictures naming (Deloche *et al.*, 1996). Four patients were not able to undergo the full battery. Complementary tests were performed according to the symptoms.

Brain imaging

Brain MRIs were available for 21/32 mutation carriers (Supplementary Table 1), and CT scans for two. These exams were visually analysed.

Brain perfusion SPECT was performed after intravenous injection of 99mTc-ECD in 10/32 mutations carriers (six fvFTD, two CBDS, one PPA, one Alzheimer's disease) in four centres using the same ECD protocol. Perfusion profiles were compared to 28 healthy age-matched controls, and also to 31 fvFTD patients with no *GRN* and no *MAPT* mutations, matched for gender, age at onset, disease duration and behavioural profile at onset (disinhibition, apathy, mixed). Details on each group are available in Supplementary Table 2.

A voxel-by-voxel intergroup comparison was performed with SPM2. The centre effect was minimized by filtering and masking as previously described (Le Ber *et al.*, 2006; Guedj *et al.*, 2007). Significant hypoperfusion in the group of mutations carriers was looked for first in comparison to healthy subjects, then to non-carriers. SPM{T} maps of the mutation carriers were thus compared to those of healthy subjects at a height threshold of $P = 0.05$, corrected for multiple comparisons for the cluster. Then, areas with significant hypoperfusion in mutation carriers were compared to the same regions in non-carrier patients, using a height threshold corrected for multiple comparisons for the voxel (False Discovery Rate method, FDR). Interhemispheric asymmetry was then evaluated visually in the two groups of patients.

The same statistical threshold was used for additional voxel-based analyses, including, (i) subjects of the same centre (Pitié-Salpêtrière) with SPECT performed with the same gamma-camera (five *GRN* mutation carriers; seven fvFTD patients with no mutations matched for gender, age at onset, disease duration, behavioural profile, and 16 healthy age-matched controls); (ii) six *GRN* mutation carriers with fvFTD (excluding patients with CBDS, PPA, Alzheimer's disease) in comparison to 20 fvFTD patients with no mutations, matched for gender, age at onset, disease duration, behavioural profile and to 28 healthy age-matched controls.

Results

Mutations in GRN

We identified 18 *GRN* null mutations, seven of which were novel (Table 2), in 24 independently ascertained probands and in eight affected relatives (32 mutation carriers). In addition, we found mutations in two relatives of F716/001, one asymptomatic at age 60 and one with schizophrenia.

Nineteen probands had autosomal dominant inheritance. Five (F001/001, F057/007, F263/001, F583/001, F587/006) had no family history of the disease. Their parents were deceased, without neurological disorders, after age 65 (except for one). DNA was not available, so we could not distinguish between reduced penetrance in the transmitting parent and *de novo* mutations.

Ten small deletions/insertions causing frameshifts, three nonsense mutations and three splice site mutations (Table 2), all leading to premature termination codons, were predicted to result in haploinsufficiency (Baker *et al.*, 2006). We also found a mutation in the initiation codon (c.1A>G, p.Met1?) that segregated with the disease in family F716, and a missense mutation (c.19T>C, p.Trp7Arg) in the signal peptide of the protein. None of these mutations were found in 179 French controls. Segregation with the disease was confirmed in eight families. The most frequent mutation, p.Glu498fsX11, was detected in three families, and four mutations were identified in two families each (Table 2). There were no *GRN* gene copy number variations.

No mutations were found in 3/11 relatives with dementia from three families (F124, F171, F741). They were also

Table 2 *GRN* mutations detected in 24 families

Families	Mutation		
	Genome[a]	Predicted RNA[b]	Predicted protein[c]
F587	g.96239A>T	–	p.0
F716[d]	g.100067A>G	c.1A>G	p.Met1 ?
F128[d]	g.100085T>C	c.19T>C	p.Trp7Arg
F043[d]	g.101108C>T	c.328C>T	p.Arg110X
F047[d]	g.101130delG	c.350delG	p.Gly117ValfsX138
F015	g.120141delG	c.361delG	p.Val121TrpfsX135
F522	g.101160_101161delCT	c.380_381delCT	p.Pro127ArgfsX2
F521	g.101164_101167delTAGT	c.384_387delTAGT	p.Gln130SerfsX125
F129[d]	g.101342A>C	c.463-2A>C	p.Ala155TrpfsX56
F583	g.101349_101355delCTGCTGT	c.468_474delCTGCTGT	p.Cys157LysfsX97
F001, F329	g.101703G>A	c.599_708del	p.Val200GlyfsX18
F050	g.101983_101984delTG	c.753_754delTG	p.Cys253X
F160[d]	g.102241_102244delCACT	c.813_816delCACT	p.Leu271IfsX10
F524, F124	g.102460C>A	c.942C>A	p.Cys314X
F263	g.102613_102614delCT	c.1095_1096delCT	p.Cys366fsX1
F171, F258	g.102938C>T	c.1201C>T	p.Gln401X
F057, F331	g.102969_102970insGT	c.1232_1233insGT	p.Ala412fsX1
F540, F741, F023[d]	g.103323_103327delAGTGG	c.1494_1498delAGTGG	p.Glu498fsX11

[a]Numbered relative to the reverse complement of GenBank Accession Number AC003043 and starting at nt 1. [b]Numbered according to the largest GRN transcript (GenBank Accession Number NM.002087.2) and starting at translation initiation codon. [c]Numbered according to the largest GRN isoform (GenPept Accession Number NP.002078.1). [d]Families with novel mutations.

negative for *MAPT* mutations. Notably, a branch of family F171 had autosomal dominant FTD-MND (Supplementary Fig. 1), but no *GRN* mutations. No mutations were found either in a sister of F741/007 who had dementia with frontal symptoms and a sister of the proband in family F124 who had dementia at age 64.

Frequency of GRN mutations in probands with fvFTD, PPA, CBDS and FTD-MND

The frequency of mutations in fvFTD, PPA, CBDS and FTD-MND was calculated using the number of probands with identified mutations in each disease category (Table 1). The frequency of *GRN* mutations was 5.7% (20/352) in fvFTD (17.9% in those with autosomal dominant inheritance, 19/106), 4.4% (3/68) in PPA and 3.3% (1/30) in CBDS. No mutations were found in the 52 probands with FTD-MND.

Phenotype in mutation carriers

Clinical data were collected for 32 mutation carriers (24 probands, eight relatives). There were 13 males and 19 females (Table 3).

Disease onset

The mean age at onset was 59.1 ± 7.7 years (49–79). Age at onset was >65 years in 7/32 (22%), and was variable among and within families.

At onset, 24/32 (75%) had marked behavioural disorders, 7/32 (22%) had language disorders and 3/32 (9%) memory disorders (Table 3). The mean disease duration at the first consultation in a memory disorders clinic was 3.0 ± 2.1 years.

Description of the mutation carriers according to the phenotype

Patients with fvFTD (n = 22). Twenty-two mutation carriers had fvFTD (20 probands, two relatives). Diagnosis of fvFTD was made at onset in 18 probands and two relatives (20/32, 63%). Two (F171/002, F263/001) had aphasia with behavioural disorders at onset. One proband (F524/001) with fvFTD initially had a psychiatric presentation, with visual and auditory hallucinations and severe paranoid delusions.

In two other probands (2/32, 6%) (F057/007, F050/001), Lewy body dementia (LBD) was initially suspected because of hallucinations and/or parkinsonism at onset. The diagnosis changed to fvFTD by the time of inclusion, and they were included as such.

Patients with PPA (n = 5/32, 16%). Five mutation carriers including three probands and two relatives had PPA (Mesulam, 2001). They had severe language disorders at onset and no behavioural disorders during the first 2 years of the disease.

Patients with CBDS (n = 2/32, 6%). Mutations were found in one proband and her sister who had CBDS according to clinical criteria (Boeve *et al.*, 2006). They had behavioural symptoms at onset, but rapidly developed asymmetric parkinsonian rigidity, left upper limb apraxia and hemineglect; one had dystonia.

Patients with other diagnoses (n = 3/32, 9%). Three affected relatives (F015/010, F129/002, F160/019) with proven *GRN* mutations had been diagnosed with Alzheimer's disease in a memory disorders clinic. They had predominant episodic memory disorders as the

Table 3 Main clinical and behavioural characteristics of 32 *GRN* mutation carriers

Families/ Patients Proband/ Relative	Age at onset (years)	Age at first examination (years)	Initial diagnosis	Signs at onset	Main behavioural disorders in the disease course	Language and speech disorders	Apraxia and parietal symptoms	Park.	Hallucinations
F001/001[a] Proband	53	58	fvFTD	Behavioural disorders	Apathy, loss of interest	Reduction of spontaneous language	na	–	–
F015/008 Proband	56	61	fvFTD	Apathy, behavioural, attention and memory disorders	Apathy, loss of interest, attention deficit aggressiveness, personality changes	Reduction of spontaneous language, echolalia, palilalia	CD	+	V
F015/010 Relative	49	52	AD	Memory disorders	–	Mild word finding difficulties	–	–	–
F023/004 Proband	52	54	PPA	Language disorders	Language disorders	Reduced fluency with semantic paraphasias, without agrammatism	CD	–	–
F043/001 Proband	56	59	fvFTD	Behavioural disorders	Apathy, reduction of activities, attention disorders, bulimia, motor stereotypies	Reducted fluency, semantic paraphasias, verbal comprehension deficit	IM, CD, I, D, acalculia	–	V
F047/001 Proband	69	72	PPA	Language disorders	Physical neglect, hyperorality, disinhibition	Progressive nonfluent aphasia, verbal comprehension deficit	–	–	–
F050/001 Proband	61	63	LBD/fvFTD	Behavioural disorders	Loss of interest, loss of personal care, bulimia, stereotype, disinhibition	–	–	+	V
F057/007 Proband	61	64	LBD/fvFTD	Bulimia, behavioural disorders, tachyphemia	Verbal and sexual disinhibition, joviality, bulimia, apathy, attention disorders, emotional indifference	Tachyphemia, reduction of spontaneous language, echolalia, palilalia	–	–	V
FI24/005 Proband	69	77	fvFTD	Behavioural disorders	Apathy, behavioural disorders	–	na	+	–
FI28/001 Proband	51	53	fvFTD	Attention disorders	Attention disorders distractivity, imitation, indifference	–	CD	+	–
FI29/001 Proband	60	62	fvFTD	Behavioural disorders and apraxia	Apragmatism, inertia, distractivity, perseverative behaviours, disinhibition, bulimia	Reduction of spontaneous language	IM, D	–	V
FI29/002 Relative	79	82	AD	Memory disorders	–	–	CD	–	–
FI60/001[a] Proband	66	70	fvFTD	Behavioural disorders, disinhibition, social withdrawal	Disinhibition, coarseness, rituals and stereotypies, hyperorality, apathy, neglect of hygiene	Reduction of spontaneous language, echolalia	–	+	V
FI60/019 Relative	56	58	AD	Memory disorders	Rituals	–	–	–	–
FI71/001 Proband	54	57	fvFTD	Behavioural disorders	Apathy, loss of interest, fixed ideas, ritualistic behaviours, impulsivity, attention disorders	Reduction of spontaneous language	IM, D, CD Left spatial, motor and sensory neglect, visual agnosia	–	–
FI71/002[a] Relative	55	58	fvFTD with severe aphasia	PNFA, behavioural disorders and apraxia	Apathy, joviality, gluttony, bulimia, emotional lability	Non-fluent aphasia with agrammatism, echolalia	CD, agraphic apraxia, dyscalculia	+	–
FI71/004 Relative	63	69	PPA	Language disorders	Language disordersapathy, stereotypies	Conduction aphasia: non-fluent aphasia, phonemic paraphasias, impaired repetition, preserved comprehension	CD, IM	+	–

(continued)

Table 3 Continued

Families/ Patients Proband/ Relative	Age at onset (years)	Age at first examination (years)	Initial diagnosis	Signs at onset	Main behavioural disorders in the disease course	Language and speech disorders	Apraxia and parietal symptoms	Park.	Hallucinations
F258/001 Proband	60	61	PPA	Language disorders	Attention deficit, reduction of interest	Fluent aphasia with comprehension deficit	–	–	–
F263/001 Proband	74	76	fvFTD with severe aphasia	Stuttering, speech apraxia	Apathy, altered social conduct, loss of hygiene, disinhibition	Progressive nonfluent aphasia with agrammatism and speech apraxia	CD, IM	–	–
F329/001 Proband	63	64	fvFTD	Tachyphemia	Attention disorders, impulsivity, joviality, memory deficit, indifference to others	Tachyphemia	–	–	–
F331/001[a] Proband	54	64	fvFTD	Disinhibition, bulimia	Disinhibition, errotomania, joviality, aggressiveness, sexual disinhibition, loss of interest, bulimia	Logorrhoea, then reduction of spontaneous language	–	–	–
F521/010 Proband	45	47	fvFTD	Behavioural and personality changes	Apathy, attention deficit, bulimia, loss of hygiene, loss of interest	Reduction of spontaneous language, echolalia	–	–	–
F522/006 Proband	55	56	fvFTD	Behavioural disorders	Reduction of activities, agressivity, disorientation	na	–	–	–
F524/001 Proband	72	74	fvFTD	Visual hallucinations, delusions	Agitation, delusions of persecutions, paranoid ideas, obsessive behaviours, verbal disinhibition, verbal stereotypies	Logorrhoea	Prosopagnosia	–	V, A
F540/001 Proband	56	59	CBDS	Behavioural disorders	Apathy, loss of interest, attention deficit, fixed ideas, excessive spending, bulimia, gluttony	Reduction of spontaneous language	CD, Visual agnosia, spatial and motor neglect	+	–
F540/002 Proband	69	71	CBDS	Behavioural disorders and L parkinsonian rigidity	Apathy, irritability, joviality, temporal disorientation	Reduction of spontaneous language	CD, L spatial, sensory and motor neglect	+	–
F583/001 Proband	54	58	fvFTD	Behavioural disorders	Apathy, bulimia, gluttony, perseverations, disinhibition, loss of personal care, sterotypies	Reduction of spontaneous language, echolalia, palilalia, vocalisations	na	+	–
F587/006 Proband	58	63	fvFTD	Behavioural disorders	Delusional jealousy, excessive spending, apathy, social withdrawal, reduction of affect, bulimia, gluttony	Reduction of spontaneous language	–	+[l]	V
F716/001 Proband	55	57	fvFTD	Language and behavioural disorders	Loss of interest, indifference, reduction of affect, verbal stereotypies, bulimia	Reduction of spontaneous language, echolalia, palilalia	–	–	–
F716/002 Relative	55	57	PPA	Language disorders	Language disorders	Fluent aphasia with comprehension deficit	–	–	–
F741/007 Proband	57	58	fvFTD	Behavioural disorders	Apathy, sexual disinhibition, hyperorality, personal neglect	Reduction of spontaneous language	–	+	–
741/041[a] Relative	54	56	fvFTD	Behavioural disorders	Hyperorality, compulsive behaviours	Logorrhoea, then reduction of spontaneous language, echolalia, palilalia	IM, D, L spatial neglect	+	–

na = not available; A = auditory hallucinations; AD = Alzheimer's disease; CBDS = corticobasal syndrome; D = dressing apraxia; fvFTD = frontal variant of FTD; I = ideational apraxia; IM = ideomotor apraxia; L = left; LBD = Lewy body dementia; Park. = parkinsonian syndrome; PPA = primary progressive aphasia; V = visual hallucinations; CD = constructional disorders; – = absent. [a]Diagnosis of FTLD-U confirmed neuropathologically.

first symptom, and no or mild behavioural disorders at onset (Table 3). Their neuropsychological profiles (FRCT) were consistent with a hippocampal amnestic syndrome.

Members of family F716 presented with fvFTD (F716/001) or PPA (F716/002). One mutation carrier (F716/005) had schizophrenia but no dementia or language disorders. His cousin also had schizophrenia, but we could not confirm the presence of the mutation. Since the relation between schizophrenia and *GRN* mutations remains speculative, we did not include patient F716/005 or his cousin in the phenotypic study.

In summary, the clinical diagnosis at onset was fvFTD in 63% (20/32) of the mutation carriers, PPA in 16% (5/32), Alzheimer's disease in 9% (3/32), CBDS and LBD each in 6% (2/32) of the mutation carriers. Illustrative case reports are presented as Supplementary data.

There were no obvious phenotype-genotype correlations. In particular, the phenotype associated with mutation p.Trp7Arg was that of fvFTD. Families with the most frequent mutation (p.Glu498fsX11) presented either CBDS (F540), fvFTD (F741) or PPA (F023) (Table 2). The diagnoses were also variable within families (Table 3) reflecting the great intra-familial phenotype variability.

Main characteristics and progression of the disease

Twenty-eight of the 32 patients (88%) had behavioural disorders during the course of the disease (Table 3): all of the patients with fvFTD and CBDS, but also the three mutation carriers with PPA (F171/004, F258/001, F047/001) with the longest disease durations. Patients diagnosed with Alzheimer's disease may have had mild behavioural symptoms (F160/019), but they were less predominant than the memory disorders. Behavioural changes included apathy (22/32, 69%), disinhibition (10/32, 31%), hyperorality (15/32, 47%) and ritualistic/stereotyped behaviours (9/32, 28%). Twenty of the 32 patients (63%) had reduced spontaneous language, consistent with frontal dysfunction. Mutism developed after a mean disease duration of 4.1 ± 1.4 years.

Parkinsonism developed in 13/32 (41%) but was present at onset in only one patient (F540/002). Parkinsonism was observed in 10/22 patients with fvFTD (41%), 2/2 with CBDS and 1/5 with PPA (20%). Visual hallucinations (animals, people) were present in 8/32 patients (25%). None developed MND.

The mean disease duration when patients became bedridden was 4.9 ± 0.9 years ($n = 9$). Twenty patients died after mean disease durations of 6.5 ± 1.9 years. The diagnosis of FTLD-U was confirmed in five autopsied patients with fvFTD (F001/001, F160/001, F171/002, F331/001, F741/041). There were characteristic neuronal intranuclear and cytoplasmic ubiquitin- and TDP-43-positive inclusions. There were no abnormal tau, synuclein and β-amyloid deposits (Supplementary data).

Table 4 Mean neuropsychological scores of 22 *GRN* mutation carriers

Neuropsychological tests	Mean ± SD	Range
MMS (Folstein *et al.*, 1975)		
Total score (/30)	21.0 ± 5.6	9–28
Orientation (/10)	6.8 ± 2.8	0–10
Attention (/5)	2.8 ± 1.8	0–5
Encoding (/3)	2.7 ± 0.9	0–3
Recall (/3)	1.2 ± 1.1	0–3
Language (/8)	6.8 ± 1.8	3–8
Praxies (/1)	0.4 ± 0.5	0–1
MDRS (Mattis, 1988)		
Total score (/144)	114.4 ± 14.0	85–141
Initiation (/37)	23.4 ± 6.8	9–32
Verbal	19.1 ±3.8	14–24
Motor	6.3 ± 0.8	5–7
Concept (/39)	32.3 ± 5.1	25–39
Attention (/37)	32.3 ± 7.9	8–37
Construction (/6)	4.1 ±2.4	0–6
Memory (/25)	19.4 ± 4.5	13–25
Fluency tasks (Thuillard and Assal, 1991)		
Categories (animals)	12.8 ± 7.0	5–27
Letter (P/R)	5.6 ± 5.1	1–13
FAB (Dubois *et al.*, 2000)		
Total score (/18)	9.3 ± 3.6	3–14
FCRT (Van der Linden *et al.*, 2004)		
Free recall (/48)	16.3 ± 9.0	0–30
Total recall (/48)	38.1 ±11.0	11–48
Delayed free recall (/16)	6.5 ± 4.3	0–12
Delayed total recall (/16)	13.5 ± 3.7	3–16
Number of intrusions	3.0 ± 6.7	0–18

The mean disease duration at evaluation was 2.4 ± 1.2 years.

Neuropsychological characteristics

The mean scores in 22 mutation carriers are shown in Table 4. The mean disease duration at evaluation was 2.4 ± 1.2 years (Tables 4 and 5). All but two patients presented mild to severe frontal cognitive dysfunction. Episodic memory was impaired in 16/18 patients (89%) evaluated with the FCRT. Most patients (11/18, 61%) had episodic memory disorders characterized by impaired encoding and retrieval that benefited significantly from semantic cueing. This profile is consistent with frontal lobe dysfunction (Pillon *et al.*, 1994). Five (28%) however, had an amnesic syndrome with severely impaired storage consistent with hippocampal dysfunction, but executive functions were less severely or not impaired (Dubois and Albert, 2004).

Language was severely affected in a subset of patients, and five had PPA (Mesulam, 2001). One (F023/004) had progressive non-fluent aphasia with agrammatism (Mesulam, 2001) and one (F171/004) had non-fluent aphasia with impaired repetition, phonemic paraphasias and preserved comprehension, compatible with conduction aphasia (Mendez *et al.*, 2003). Two patients (F258/001, F716/002) had fluent aphasia with impaired comprehension (verbal semantic deficit). Two others (F171/002, F263/001) had characteristics of non-fluent aphasia with agrammatism

Table 5 Main neuropsychological profiles in *GRN* mutation carriers

Patients	Disease duration at examination	Main disorders (diagnosis)	Episodic memory disorders	Semantic disorders	Aphasia	Signs of parietal dysfunction
Patients with isolated frontal behavioural and cognitive syndrome (mean disease duration 2.3 years)						
F057/007	1	Behavioural (fvFTD)	Frontal type	–	(Reduction of spontaneous language)	–
F521/010	2	Behavioural (fvFTD)	Frontal type	–	(Reduction of spontaneous language)	–
F587/006	5	Behavioural (fvFTD)	Frontal type	–	–	–
F741/007	2	Behavioural (fvFTD)	Frontal type	Possible	(Reduction of spontaneous language)	na
F716/001	2	Behavioural (fvFTD)	Frontal type	Present	(Reduction of spontaneous language)	–
F329/001	2	Behavioural (fvFTD)	Frontal type	–	–	–
Patients with frontal syndrome and parietal signs (mean disease duration: 2.8 years)						
F043/001	3	Behavioural (fvFTD)	Frontal type	na	Reduced fluency, semantic paraphasias, verbal comprehension deficit	Constructional disorders ideomotor, ideational and dressing apraxia
F263/001	3	Behavioural and language (fvFTD)	na	–	PNFA with agrammatism and speech apraxia	Constructional disorders
FI28/001	3	Behavioural (fvFTD)	Frontal type	–	–	Constructional disorders
FI71/001	3	Behavioural (fvFTD)	–	–	(Reduction of spontaneous language)	Ideomotor and dressing apraxia, Constructional disorders, L spatial, sensory and motor hemi-neglect, visual agnosia
FI71/002	2	Behavioural and language (fvFTD)	Frontal type	–	PNFA with agrammatism	Apraxic agraphia, constructional disorders, dyscalculia
FI29/001	2	Behavioural (fvFTD)	na	–	(Reduction of spontaneous language)	Ideomotor and dressing apraxia
F540/002	3	CBS	Frontal type	–	(Reduction of spontaneous language)	ideomotor apraxia and constructional disorders L spatial, sensory, motor hemineglect
F540/001	3	CBS	Frontal type	–	(Reduction of spontaneous language)	Constructional disorders, Left spatial and motor hemineglect, visual agnosia
Patients with amnestic hippocampal syndrome (mean disease duration 2.5 years)						
F015/010	2	Memory disorders (AD)	Hippocampal type	–	Mild word finding difficulties	–
FI29/002	1	Memory disorders (AD)	Hippocampal type	–	–	Constructional disorders
FI60/019	2	Memory disorders (AD)	Hippocampal type	–	–	–
F524/001	2	Psychiatric presentation (fvFTD)	Hippocampal type	Prosopagnosia Semantic verbal deficit	–	–
Patients with progressive aphasia at onset (mean disease duration: 2.5 years)						
FI71/004	3	Language (PPA)	na	–	Conduction aphasia (phonemic paraphasias, impaired repetition, preserved comprehension)	Ideomotor apraxia and constructional disorders Spatial working memory impaired
F716/002	3	Language (PPA)	na	na	Fluent aphasia with comprehension (verbal semantic) deficit	–
F023/004	2	Language (PPA)	–	–	Reduced fluency with semantic paraphasias, without agrammatism	–
F258/001	2	Language (PPA)	Hippocampal type	–	Fluent aphasia with comprehension (verbal semantic) deficit	Constructional disorders

na = not available; AD = Alzheimer's disease; CBDS = corticobasal syndrome; fvFTD = frontal variant of FTD; L = left; LBD = Lewy body dementia; PNFA = progressive non-fluent aphasia; PPA = primary progressive aphasia; UL = upper limb; – = absent.

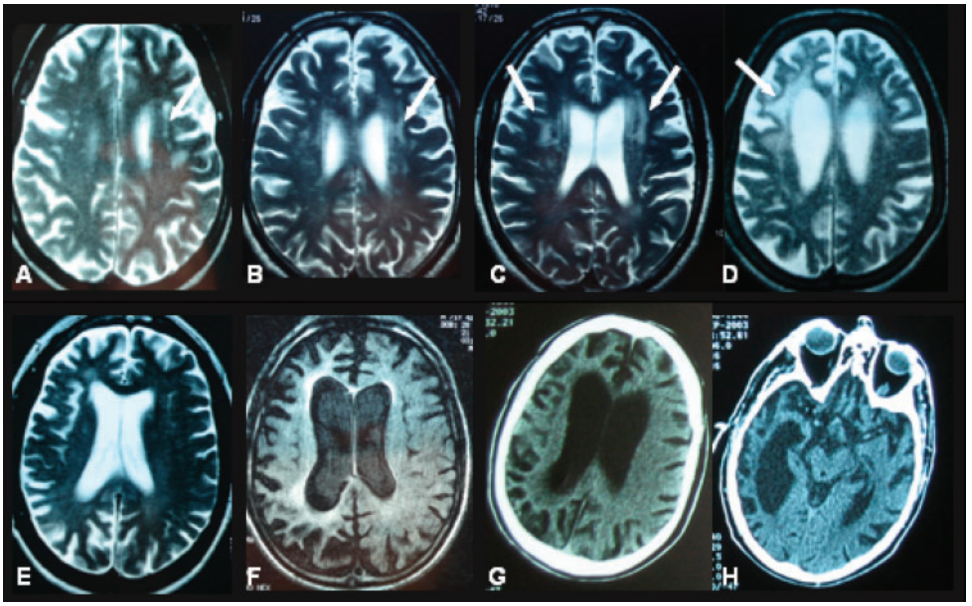

Fig. 1 Brain MRI T2 (**A–E**) and TI (**F**) sequences and CT scan (**G, H**) in *GRN* mutation carriers. (**A–D**) Moderate to marked white matter lesions (arrows). (**E–H**) Clear asymmetric and posterior atrophy.

but also marked behavioural disorders and executive syndromes at onset.

Ten out of 21 patients (48%) had constructional disorders, 24% had ideomotor apraxia (5/21) and/or agraphic apraxia (1/21). Five (45%) of these patients had a biparietal syndrome (dressing apraxia, hemineglect). None had Balint syndrome.

Four distinct neuropsychological and language profiles were therefore discernible in mutation carriers (Table 5): (i) isolated behavioural and frontal cognitive syndrome (frontal type, no sign of parietal or amnestic syndrome); (ii) fluent or non-fluent primary progressive aphasia at onset (aphasic type), only one case having an amnestic syndrome; (iii) parietal dysfunction (ideomotor apraxia, constructional disorders, neglect) associated with a frontal syndrome (parietal/apraxic type) and (iv) hippocampal amnestic syndrome associated with a mild to moderate executive dysfunction (amnestic type). The mean disease duration at evaluation was similar in each group.

Brain imaging (Supplementary Table I)

Brain MRI characteristics

MRI, performed after a mean disease duration of 2.8 ± 1.3 years showed frontal and/or temporal atrophy in all patients except one evaluated at onset (Fig. 1). Cortical atrophy was markedly asymmetric in 16/21 mutation carriers (76%), with right predominance in 10/21 (48%) and left predominance in 6/21 (29%). Parietal and/or occipital atrophy was present in 10 patients. Small patchy or more extensive white matter lesions were present on T2 sequence images in 4/21 patients (19%), in the absence of vascular risk factors.

Brain perfusion profile

SPECT, performed after a mean disease duration of 2.9 ± 1.3 years, showed significant hypoperfusion bilaterally in the fronto-cingular, the right posterior temporal cortex, including hippocampus, and the inferior parietal cortex, compared to healthy subjects ($P < 0.05$, corrected for the cluster) (Fig. 2, Supplementary Figs 2 and 3). More significant hypoperfusion compared to fvFTD patients without mutations was seen in the dorsolateral right frontal cortex, the right posterior temporal and inferior parietal cortices, the right hippocampus and the posterior cingulate cortex bilaterally ($P < 0.05$, corrected for the voxel using FDR). These functional abnormalities were also detected by visual inspection of individual SPECT examinations. There was no area in which patients with no mutations had greater hypoperfusion than *GRN* mutation carriers.

Interhemispheric perfusion asymmetry differed significantly between patients with and without mutations ($P = 0.0257$, chi-squared test). Hypoperfusion in mutation carriers predominated on the right in six patients (60%), on the left in two (20%), and was symmetric in two (20%). In patients without mutations, hypoperfusion predominated on the right in eight patients (26%), on the left in 12 (39%), and was symmetric in 11 (35%).

An intergroup analysis between centres showed no significant differences at the height threshold corrected by the FDR method used in the present study (Le Ber *et al.*, 2006). Our findings were also validated by including subjects from the same centre. Similar qualitative findings were obtained when (i) only patients investigated at the same centre or (ii) only *GRN* mutation carriers with fv-FTD phenotype were analysed (Supplementary Fig. 3).

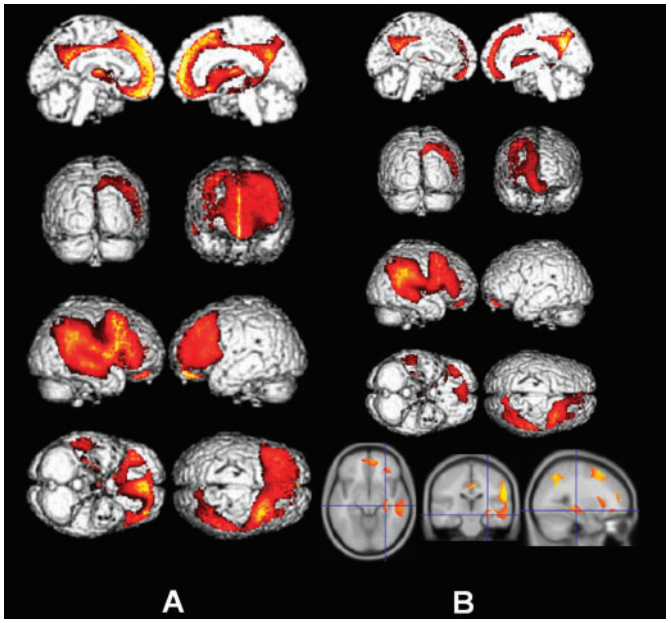

Fig. 2 Anatomical localization of peaks of hypoperfusion in: (**A**) *GRN* mutation carriers compared to healthy subjects, and (**B**) *GRN* mutation carriers compared to FTD patients without mutations (right hemisphere is on the right side of the slices). FTD patients with *GRN* mutations had significantly greater hypoperfusion in the right frontal dorsolateral cortex, right temporoparietal cortex, right hippocampus and, bilaterally, the posterior cingulate cortex, than patients without mutations.

Discussion

We have described in detail a large series of patients with different phenotypes (fvFTD, FTD-MND, PPA, CBDS) analysed for *GRN*. Previous studies on large series evaluated the genetic contribution of *GRN* mutations in FTD (Gass *et al.*, 2006), or the neuropathological aspects of this disease (Mackenzie, 2007). Two series, based on pathological examination of FTLD-U cases, included basic clinical data collected retrospectively in smaller numbers of patients (Josephs *et al.*, 2007; Davion *et al.*, 2007). In a study that screened only for the *GRN* p.Arg493X mutation in patients with FTLD from North-America, 30 families had this mutation (20% of the cohort) due to a founder effect in 27 of the 30 families (Rademakers *et al.*, 2007). The clinical data in the study of Rademakers *et al.* were obtained retrospectively for 34 patients. This mutation was not found, however, in other Belgian, Dutch or Italian populations, neither in our series of French patients so far. Our study specifically focused on the phenotypic characteristics associated with progranulin mutations, including detailed neuropsychological and brain perfusion profiles not previously reported in a large group of progranulin patients that were not selected according to the mutation. Most patients were evaluated prospectively with standardized procedures, and only patients with proven mutation were included.

Eighteen pathogenic mutations, seven of which were novel, were found in 24 families ascertained independently. The most frequent type of mutations were small deletions/insertions. Nonsense, frameshift and splice site mutations leading to premature termination codons were predicted to result in haploinsufficiency through nonsense-mediated decay (Baker *et al.*, 2006). A missense mutation in the initiation codon (c.1A>G) segregated with the disease in one family. Two other mutations were previously identified in the initiation codon (Baker *et al.*, 2006; Cruts *et al.*, 2006), the first translated codon which has a crucial role in the initiation of protein translation. These mutations probably affect protein translation and cause functional progranulin haploinsufficiency. However, the level of mutant mRNA in a brain sample from a patient with the c.2T>C mutation was reduced, suggesting that the mutant mRNA may be degraded (Baker *et al.*, 2006). We found another missense mutation in the progranulin signal peptide sequence (p.Trp7Arg) that translocates proteins to be secreted into the lumen of the endoplamic reticulum. Mutations in the peptide signal presumably lead to functional haploinsufficiency by a mislocalization of the protein or inefficient trafficking through the secretory pathway (Gass *et al.*, 2006; Mukherjee *et al.*, 2006). Another mutation in the signal peptide (p.Ala9Asp) was previously reported in four families (Gass *et al.*, 2006; Mukherjee *et al.*, 2006; Spina *et al.*, 2007*a*), including the large HDDD2 family in which the mutation segregated with the disease and a family with CBDS (Spina *et al.*, 2007*a*). Since the level of mutant mRNA was strongly reduced in the frontal cortex of patients carrying the p.Ala9Asp mutation, it is also possible that mutations in the signal peptide induce a process similar to nonsense-mediated decay (Gass *et al.*, 2006).

Phenocopies were present in 3/24 families in our series. Autosomal dominant FTD-MND was present in a branch of family F171 with no *GRN* mutations, indicating that another gene is responsible for the disease in this branch. A similar situation was found in a large Calabrian family (Bruni *et al.*, 2007), a branch of which had FTD but no mutations. Caution should be exercised, therefore, when counselling affected members of progranulin families who do not have proven *GRN* mutations. The occurrence of two rare forms of autosomal dominant FTD in the same family is intriguing. Further studies on extended families are needed to determine whether *GRN* polymorphisms on the normal allele might enhance the risk of developing other types of FTD.

Sixty-three per cent of mutation carriers had initial clinical diagnoses of fvFTD, whereas a high proportion (37%) had another clinical diagnosis, comprising PPA, Alzheimer's disease, CBDS or LBD. These diagnoses were made in memory centres based on clinical and neuropsychological criteria. There were no correlations between the phenotype and the genotype, as expected, since all the mutations lead to progranulin haploinsufficiency.

Furthermore, no obvious modulatory effects of the *MAPT* haplotype or ApoE genotype on the clinical presentation have been observed (Gass *et al*., 2006; Bruni *et al*., 2007). In contrast, Rademakers and collaborators (2007) found an association between ApoEε4 allele with early memory disorders that were present in 30% out 37 patients with the p.Arg493X mutation. However, this study was based on a limited number of patients for which the clinical data were collected retrospectively, which possibly constitutes a bias. The effect of modifying factors on the clinical presentation of the disease should be validated in larger groups of patients in which the clinical symptoms are evaluated prospectively.

The relative frequency of *GRN* mutations was 5.7% in French patients with fvFTD, up to 17.9% in familial forms. Higher frequencies, reaching 25% of familial forms, were found in North-American and Belgian studies (Baker *et al*., 2006; Cruts *et al*., 2006). They were probably overestimated, however, partly due to a founder effect or selection of FTLD-U or 17q-linked families. Our study gives a more accurate evaluation of the frequency in a large unselected population of patients with fvFTD, with separate evaluation of FTD-MND. The frequency of *GRN* mutations in familial forms in our study is close to that evaluated by Huey and his collaborators (2006), but higher than in two smaller Dutch (4%) and Italian populations (1%) (Bruni *et al*., 2007; Bronner *et al*., 2007). These discrepancies may reflect geographical differences or may be due to different criteria for familial disease and variable proportions of patients with FTD-MND, not caused by *GRN* mutations, included in the different studies.

We evaluated separately the frequency of *GRN* mutations in patients with FTD-MND. None of the 52 patients had mutations, and none of the mutation carriers developed MND during the course of the disease. Two sequence variants (p.Arg433Trp, p.Ser120Tyr) resulting in an amino-acid substitution but not in a progranulin haploinsufficiency, have been reported in patients with FTD-MND (Schymick *et al*., 2007; Spina *et al*., 2007*b*), but their pathogenicity has not been established. They were not present in our patients with FTD-MND, but p.Arg433Trp was found in one our healthy controls, indicating that it is more probably a benign variant. Our results are in accordance with smaller studies of patients with FTD-MND (Gass *et al*., 2006; Schymick *et al*., 2007), and demonstrates that FTDU-17 and FTD-MND are distinct genetic diseases, although both are characterized by ubiquitin-positive inclusions. It is also concordant with the absence of characteristic lesions of MND (Bunina bodies, skein-like lesion) in *GRN* mutation carriers (Mukherjee *et al*., 2006; Mackenzie, 2007).

This is the first study evaluating the frequency of *GRN* mutations in patients with PPA and CBDS. *GRN* mutations were less frequent in these diseases, 4.4% and 3.3%, respectively, than in fvFTD. Although PPA and CBDS are not usually familial diseases, all these mutation carriers had at least one relative with dementia, PPA or CBDS. In contrast, there were no mutations in patients without family histories of neurodegenerative diseases. It is not surprising that we identified *GRN* mutations in our patients with PPA. This is consistent with the fact that clinically defined PPA has been shown to be pathologically heterogeneous. The most common characteristics are tau-positive or Alzheimer's disease pathology (Kertesz *et al*., 2005; Knibb *et al*., 2006; Josephs *et al*., 2006). However, a proportion of PPA patients have ubiquitin-positive inclusions (Kertesz *et al*., 2005; Josephs *et al*., 2006), as observed in progranulin patients (Cairns *et al*., 2007; Mackenzie, 2007). Our study shows that some of these patients indeed have mutations in *GRN*.

This study provides a precise description of the neurological signs associated with *GRN* mutations and evaluation of their frequency based on the prospective collection of data. Parkinsonian syndromes were frequent in our patients (41%), concordant with the observation of striatal lesions in *GRN* mutation carriers (Josephs *et al*., 2007; Mackenzie, 2007). More interesting is the presence of visual hallucinations (25%), which were much more frequent in this series than in fvFTD patients with no mutations (2%) (Le Ber *et al*., 2006), and appear to have been the first symptom in one of our patients. Hallucinations have previously been reported in a few families with *GRN* mutations (Benussi *et al*., 2006; Boeve *et al*., 2006; Leverenz *et al*., 2007), but mostly in reports of single families. Hallucinations were not evaluated in two large series of patients (Gass *et al*., 2006; Mackenzie, 2007). They appear to be much less frequent (8%) in another large series, but their frequency could be underestimated due to retrospective collection of clinical data (Rademakers *et al*., 2007). The presence of visual hallucinations in 25% of our patients shows that is an important symptom that may help differentiate patients with *GRN* mutations from other FTD patients. Their presence may sometimes lead to an erroneous diagnosis of Lewy body dementia, in particular when parkinsonian symptoms are associated. However, cognitive symptoms did not fluctuate in *GRN* mutations carriers as they do in patients with LBD. LBD-pathology was associated to FTLD-U in few *GRN* cases (Knibb *et al*., 2006; Josephs *et al*., 2007; Spina *et al*., 2007*b*). One of our five autopsied patients had hallucinations and FTLD-U, but no synuclein pathology. It is not excluded, however, that a subset of our patients with an LBD-like phenotype or hallucinations may prove to have LBD-pathology on autopsy.

A major aim of this study was to provide a description of neuropsychological characteristics associated to *GRN* mutations in carriers investigated with standardized procedures. Four different neuropsychological/language profiles were distinguished according to the predominance of frontal cognitive syndrome or language disorders at onset, and the presence of apraxic or amnestic syndromes. Importantly, these profiles do not reflect different stages of disease

progression since the disease durations were similar. More probably, they reflect different patterns of neurodegeneration, which are concordant with the localization of brain atrophy, which was asymmetric and with more severe parietal involvement in some patients.

Seven mutation carriers had aphasic disorders in our study, five with a diagnosis of PPA. A few patients with PPA due to different *GRN* mutations were previously reported (Snowden *et al.*, 2006; Mesulam *et al.*, 2007). Non-fluent aphasia was a prominent feature in many patients of a Belgian founder family (Cruts *et al.*, 2006). In contrast, a recent study found that language deficits in *GRN* mutation carriers were less frequent than FTLD-U patients with no mutations, two out of nine carriers having non-fluent or mixed aphasia (Van Deerlin *et al.*, 2007). Notably, the characteristics of aphasia were not homogeneous in our patients. Aphasia was mostly non-fluent, consistent with PPA with agrammatism (Mesulam, 2001), or with conduction aphasia (Mendez *et al.*, 2003); but fluent aphasia with a verbal semantic deficit, resembling SD (Neary *et al.*, 1998), but without agnosia, was also observed in our patients.

The high frequency of early ideomotor apraxia and constructional disorders, consistent with parietal dysfunction, is of note. Praxis is usually preserved in early stage of FTD (Neary *et al.*, 1998). Apraxia early in the course of the disease may therefore distinguish *GRN* mutation carriers from other FTD patients. The diagnosis of CBDS was made in two of our mutation carriers, because of severity of asymmetric apraxia associated with left parkinsonian signs, left hemi-neglect and frontal dysfunction. Their clinical characteristics were remarkably similar to the proganulin patients described by Masellis *et al.* (2006) although their mutations were different. The frequency of apraxia in our study suggests that posterior cortical regions are affected early in *GRN* mutation carriers. Accordingly, more severe parietal degeneration was found in *GRN* carriers compared to FTLD-U patients without mutations (Josephs *et al.*, 2007). Remarkably, there was no Balint syndrome in our patients, suggesting that the dorsal parietal network was less involved (Tang-Wai *et al.*, 2004).

The unexpected frequency of episodic memory disorders (89%) determined on the basis of neuropsychological evaluations was also a major observation and may represent a distinctive characteristic of *GRN* mutation carriers. Most of the patients had encoding and retrieval deficits but a normal storage process. This profile was consistent with frontal executive dysfunction (Pillon *et al.*, 1994). Five patients, however, had hippocampal amnestic syndrome. Three of these patients had clinical diagnoses of Alzheimer's disease made in memory centres based on clinical and neuropsychological criteria. Coexistence of FTLD-U and Alzheimer's disease pathology has occasionally been described in *GRN* carriers (Snowden *et al.*, 2006; Josephs *et al.*, 2007; Rademakers *et al.*, 2007; Spina *et al.*, 2007*b*). Neuropathological data was not available for our three patients, two of whom are still alive. Therefore, we cannot formally exclude that they had the pathological lesions of Alzheimer's disease. However, progranulin is highly expressed in the hippocampus (Daniel *et al.*, 2000), in which marked atrophy and neuronal loss may be observed in progranulin patients (Boeve *et al.*, 2006; Mukherjee *et al.*, 2006; Snowden *et al.*, 2006; Mackenzie, 2007). Neuronal degeneration was severe enough in some cases that hippocampal sclerosis was diagnosed (Boeve *et al.*, 2006; Mackenzie, 2007; Rademakers *et al.*, 2007). Accordingly, we can hypothesize that the amnestic syndrome in mutation carriers is related to hippocampal neurodegeration caused by progranulin-related disease.

A particular pattern of hypoperfusion involving the hippocampus, posterior cingulate and parietal lobe, as well as frontotemporal cortices characterizes *GRN* mutation carriers in our study. However, the small number of patients is a limitation of our study and these results should be confirmed in larger series of patients. The inferior right parietal hypoperfusion was more severe in mutation carriers than in patients without mutations. This may be related to the high frequency of apraxia in our study. A similar pattern of regional atrophy was found using voxel-based morphometry in *GRN* patients (Whitwell *et al.*, 2007). In this study, grey matter loss in the parietal lobe was a consistent finding and differentiated mutation carriers from non-carriers.

Hypoperfusion in the hippocampus was an unexpected finding, as it is not frequently observed in patients with Alzheimer's disease, a disease with severe hippocampal involvement. It was clearly present on the individual SPECT images of our progranulin patients (Supplementary Fig. 2) and statistically demonstrated by voxel-based analysis in comparison to healthy subjects and non-carrier patients. It may be related to the amnestic syndrome and hippocampal degeneration found in *GRN* mutation carriers. Perfusion studies in a larger series of patients will be necessary, however, to correlate brain perfusion and performances on neuropsychological tests.

Predominant posterior cingulate hypoperfusion was also an unexpected finding since this is known to be preferentially associated with Alzheimer's disease (Foster *et al.*, 2007). Posterior cingulate hypoperfusion in Alzheimer's disease is presumed to result from deafferentation of the medial temporal cortex (Hayashi *et al.*, 1999; Meguro *et al.*, 1999; Millien *et al.*, 2002). We hypothesize similarly that the hippocampal impairment in our patients with *GRN* mutations would explain the hypoperfusion in the cingulate cortex.

Our study illustrates the highly variable phenotypes and neuropsychological profiles associated with *GRN* mutations and provide further evidence that the phenotype is a poor predictor of the underlying histopathology. These variable phenotypes and neuropsychological profiles, as well as the brain perfusion profiles, may reflect different patterns of neurodegeneration in progranulin disease. Since all the

mutations led to a progranulin haploinsufficiency, they would not in themselves be responsible for the phenotypic variability. Other modifying factors may therefore play a major role in determining the age at onset, the distribution and progression of brain damage and, thus, the clinical presentation of the disease.

Supplementary material

Supplementary material is available at *Brain* online.

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References

Ahmed Z, Mackenzie IR, Hutton ML, Dickson DW. Progranulin in frontotemporal lobar degeneration and neuroinflammation. J Neuroinflammation 2007; 4: 7.

Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; 442: 916–9.

Behrens MI, Mukherjee O, Tu PH, Liscic RM, Grinberg LT, Carter D, et al. Neuropathologic heterogeneity in HDDD1: a familial frontotemporal lobar degeneration with ubiquitin-positive inclusions and progranulin mutation. Alzheimer Dis Assoc Disord 2007; 21: 1–7.

Benussi L, Binetti G, Sina E, Gigola L, Bettecken T, Meitinger T, et al. A novel deletion in progranulin gene is associated with FTDP-17 and CBS. Neurobiol Aging 2006 Dec 5; [Epub ahead of print].

Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol 2003; 54 (Suppl 5): S15–9.

Boeve BF, Baker M, Dickson DW, Parisi JE, Giannini C, Josephs KA, et al. Frontotemporal dementia and parkinsonism associated with the IVS1+1G→A mutation in progranulin: a clinicopathologic study. Brain 2006; 129: 3103–14.

Bronner IF, Rizzu P, Seelaar H, van Mil SE, Anar B, Azmani A, et al. Progranulin mutations in Dutch familial frontotemporal lobar degeneration. Eur J Hum Genet 2007; 15: 369–74.

Bruni AC, Momeni P, Bernardi L, Tomaino C, Frangipane F, Elder J, et al. Heterogeneity within a large kindred with frontotemporal dementia: a novel progranulin mutation. Neurology 2007; 69: 140–7.

Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol (Berl). 2007; 114: 5–22.

Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006; 442: 920–4.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44: 2308–14.

Daniel R, He Z, Carmichael KP, Halper J, Bateman A. Cellular localization of gene expression for progranulin. J Histochem Cytochem 2000; 48: 999–1009.

Davion S, Johnson N, Weintraub S, Mesulam MM, Engberg A, Mishra M, et al. Clinicopathologic correlation in PGRN mutations. Neurology 2007; 69: 1113–21.

Deloche G, Hannequin D, Dordain M, Perrier D, Pichard B, Quint S, et al. Picture confrontation oral naming: performance differences between aphasics and normals. Brain Lang 1996; 53: 105–20.

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology 2000; 55: 1621–6.

Dubois B, Albert ML. Amnestic MCI or prodromal Alzheimer's disease? Lancet Neurol 2004; 3: 246–8.

Folstein MF, Folstein SE, Mc Hugh PR. Mini Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 2007; 130: 2616–35.

Gass J, Cannon A, Mackenzie IR, Boeve B, Baker M, Adamson J, et al. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Hum Mol Genet 2006; 15: 2988–3001.

Guedj E, Le Ber I, Lacomblez L, Dubois B, Verpillat P, Didic M, et al. Brain spect perfusion of frontotemporal dementia associated with motor neuron disease. Neurology 2007; 69: 488–90.

Hayashi T, Fukuyama H, Katsumi Y, Hanakawa T, Nagahama Y, Yamauchi H, et al. Cerebral glucose metabolism in unilateral entorhinal cortex-lesioned rats: an animal PET study. Neuroreport 1999; 10: 2113–8.

Huey ED, Grafman J, Wassermann EM, Pietrini P, Tierney MC, Ghetti B, et al. Characteristics of frontotemporal dementia patients with a Progranulin mutation. Ann Neurol 2006; 60: 374–80.

Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5′-splice site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393: 702–5.

Josephs KA, Petersen RC, Knopman DS, Boeve BF, Whitwell JL, Duffy JR, et al. Clinicopathological analysis of frontotemporal and corticobasal degenerations and PSP. Neurology 2006; 66: 41–8.

Josephs KA, Ahmed Z, Katsuse O, Parisi JF, Boeve BF, Knopman DS, et al. Neuropathologic features of frontotemporal lobar degeneration with ubiquitin-positive inclusions with progranulin gene (PGRN) mutations. J Neuropathol Exp Neurol 2007; 66: 142–51.

Kertesz A, Davidson W, Munoz DG. Clinical and pathological overlap between frontotemporal dementia, primary progressive aphasia and corticobasal degeneration: the Pick complex. Dement Geriatr Cogn Disord 1999; 10 (Suppl 1): 46–9.

Kertesz A, Nadkarni N, Davidson W, Thomas AW. The frontal behavioral inventory in the differential diagnosis of frontotemporal dementia. J Int Neuropsychol Soc 2000; 6: 460–8.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain 2005; 128: 1996–2005.

Knibb JA, Xuereb JH, Patterson K, Hodges JR. Clinical and pathological characterization of progressive aphasia. Ann Neurol 2006; 59: 156–65.

Lebert F, Pasquier F, Souliez L, Petit H. Frontotemporal behavioural scale. Alzheimer Dis Assoc Disord 1998; 12: 335–9.

Le Ber I, Guedj E, Gabelle A, Verpillat P, Volteau M, Thomas-Anterion C, et al. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. Brain 2006; 129: 3051–65.

Le Ber I, van der Zee J, Hannequin D, Gijselinck I, Campion D, Puel M, et al. Progranulin null mutations in both sporadic and familial frontotemporal dementia. Hum Mutat 2007; 28: 846–55.

Leverenz JB, Yu CE, Montine TJ, Steinbart E, Bekris LM, Zabetian C, et al. Novel progranulin mutation associated with variable clinical presentation and tau, TDP43 and alpha-synuclein pathology. Brain 2007; 130: 1360–74.

Mackenzie IR. The neuropathology and clinical phenotype of FTD with progranulin mutations. Acta Neuropathol 2007; 114: 49–54.

Masellis M, Momeni P, Meschino W, Heffner R Jr, Elder J, Sato C, et al. Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. Brain 2006; 129: 3115–23.

Mattis S. Dementia Rating Scale. Odessa (FL): Psychological assessment resources; 1988.

Meguro K, Blaizot X, Kondoh Y, Le Mestric C, Baron JC, Chavoix C. Neocortical and hippocampal glucose hypometabolism following neurotoxic lesions of the entorhinal and perirhinal cortices in the non-human primate as shown by PET. Implications for Alzheimer's disease. Brain 1999; 122: 1519–31.

Mendez MF, Clark DG, Shapira JS, Cummings JL. Speech and language in progressive nonfluent aphasia compared with early Alzheimer's disease. Neurology 2003; 61: 1108–13.

Mesulam MM. Primary progressive aphasia. Ann Neurol 2001; 49: 425–32.

Mesulam M, Johnson N, Krefft TA, Gass JM, Cannon AD, Adamson JL, et al. Progranulin mutations in primary progressive aphasia: the PPA1 and PPA3 families. Arch Neurol 2007; 64: 43–7.

Millien I, Blaizot X, Giffard C, Mezenge F, Insausti R, Baron JC, et al. Brain glucose hypometabolism after perirhinal lesions in baboons: implications for Alzheimer disease and aging. J Cereb Blood Flow Metab 2002; 22: 1248–61.

Mukherjee O, Pastor P, Cairns NJ, Chakraverty S, Kauwe JS, Shears S, et al. HDDD2 is a familial frontotemporal lobar degeneration with ubiquitin-positive, tau-negative inclusions caused by a missense mutation in the signal peptide of progranulin. Ann Neurol 2006; 60: 314–22.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546–54.

Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 2006; 314: 130–3.

Pillon B, Deweer B, Michon A, Malapani C, Agid Y, Dubois B. Are explicit memory disorders of progressive supranuclear palsy related to damage to striatofrontal circuits? Comparison with Alzheimer's, Parkinson's, and Huntington's diseases. Neurology 1994; 44: 1264–70.

Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann Neurol 1998; 43: 815–25.

Rademakers R, Baker M, Gass J, Adamson J, Huey ED, Momeni P, et al. Phenotypic variability associated with progranulin haploinsufficiency in patients with the common 1477C→T (Arg493X) mutation: an international initiative. Lancet Neurol 2007; 6: 857–68.

Rey A. Test de copie et de reproduction de mémoire de figures géométriques complexes. Paris: ECPA; 1959.

Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, et al. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. Nat Genet 2006; 38: 24–6.

Schymick J, Yang Y, Andersen P, Vonsattel JP, Greenway M, Momeni P, et al. Progranulin mutations and ALS or ALS-FTD phenotypes. J Neurol Neurosurg Psychiatry 2007; 78: 754–6.

Snowden JS, Pickering-Brown SM, Mackenzie IR, Richardson AM, Varma A, Neary D, et al. Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. Brain 2006; 129: 3091–102.

Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. Proc Natl Acad Sci USA 1998; 95: 7737–41.

Spina S, Murrell JR, Huey ED, Wassermann EM, Pietrini P, Grafman J, et al. Corticobasal syndrome associated with the A9D Progranulin mutation. J Neuropathol Exp Neurol 2007a; 66: 892–900.

Spina S, Murrell JR, Huey ED, Wassermann EM, Pietrini P, Baraibar MA, et al. Clinicopathologic features of frontotemporal dementia with progranulin sequence variation. Neurology 2007b; 68: 820–7.

Tang-Wai DF, Graff-Radford NR, Boeve BF, Dickson DW, Parisi JE, Crook R, et al. Clinical, genetic and neuropathologic characteristics of posterior cortical atrophy. Neurology 2004; 63: 1168–74.

The Lund and Manchester groups.Consensus statement: clinical and neuropathological criteria for fronto-temporal dementia. J Neurol Neurosurg Psychiatry 1994; 4: 416–8.

Thuillard F, Assal G. Données neuropsychologiques chez le sujet âgé normal. In: Habib M, Joanette Y, Puel M, editors. Démences et syndromes démentiels. Approche neuropsychologique. Paris: Masson; 1991. p. 125–33.

Van Deerlin VM, Wood EM, Moore P, Yuan W, Forman MS, Clark CM, et al. Clinical, genetic, and pathologic characteristics of patients with frontotemporal dementia and progranulin mutations. Arch Neurol 2007; 64: 1148–53.

Van der Linden M, Coyette F, Poitrenaud J, et al. L'épreuve de rappel libre/rappel indicé de 16 items (RL/RI-16). In: Van der Linden M, editor. L'évaluation des troubles de la mémoire. Solal: Marseille; 2004. p. 25–47.

van der Zee J, Le Ber I, Maurer-Stroh S, Engelborghs S, Gijselinck I, Camuzat A, et al. Mutations other than null mutations producing a pathogenic loss of progranulin in frontotemporal dementia. Hum Mutat 2007; 28: 416.

Whitwell JL, Jack CR Jr, Baker M, Rademakers R, Adamson J, Boeve BF, et al. Voxel-based morphometry in frontotemporal lobar degeneration with ubiquitin-positive inclusions with and without progranulin mutations. Arch Neurol 2007; 64: 371–6.