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ABSTRACT

Background: Frontotemporal lobar degeneration (FTLD) is a genetically and pathologically heterogeneous neurodegenerative disorder.

Methods: We collected blood samples from a cohort of 225 patients with a diagnosis within the FTLD spectrum and examined the heritability of FTLD by giving each patient a family history score, from 1 (a clear autosomal dominant history of FTLD) through to 4 (no family history of dementia). We also looked for mutations in each of the 5 disease-causing genes (*MAPT, GRN, VCP, CHMP2B,* and *TARDP*) and the *FUS* gene, known to cause motor neuron disease.

Results: A total of 41.8% of patients had some family history (score of 1, 2, 3, or 3.5), although only 10.2% had a clear autosomal dominant history (score of 1). Heritability varied across the different clinical subtypes of FTLD with the behavioral variant being the most heritable and frontotemporal dementia–motor neuron disease and the language syndromes (particularly semantic dementia) the least heritable. Mutations were found in *MAPT* (8.9% of the cohort) and *GRN* (8.4%) but not in any of the other genes. Of the remaining patients without mutations but with a strong family history, 7 had pathologic confirmation, falling into 2 groups: type 3 FTLD-TDP without *GRN* mutations (6) and FTLD-UPS (1).

Conclusion: These findings show that frontotemporal lobar degeneration (FTLD) is a highly heritable disorder but heritability varies between the different syndromes. Furthermore, while *MAPT* and *GRN* mutations account for a substantial proportion of familial cases, there are other genes yet to be discovered, particularly in patients with type 3 FTLD-TDP without a *GRN* mutation. *Neurology*® 2009;73:1451–1456

GLOSSARY

bvFTD = behavioral variant frontotemporal dementia; **CBS** = corticobasal syndrome; **FTLD** = frontotemporal lobar degeneration; **LPA** = logopenic/phonologic variant of primary progressive aphasia; **MND** = motor neuron disease; **PNFA** = progressive nonfluent aphasia; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **SemD** = semantic dementia.

Frontotemporal lobar degeneration (FTLD) is a genetically and pathologically heterogeneous degenerative disorder.[1,2] A number of different clinical syndromes fall into the FTLD spectrum: the most common subtype consists of patients who present with behavioral or personality changes (behavioral variant frontotemporal dementia or bvFTD). Less commonly, patients present with language impairment and 3 different disorders are described (often under the collective term primary progressive aphasia or PPA): semantic dementia (SemD), progressive nonfluent aphasia (PNFA), and the logopenic/phonologic variant of PPA (LPA).[3,4] There is also an overlap of FTLD with motor disorders: the parkinsonian disorders, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) and motor neuron disease (known as FTD-MND when there is an overlap).[5,6] FTLD is commonly familial[7] and 5 genes are currently known to cause FTLD, of which 2 are relatively common (microtubule-associated pro-

tein tau, *MAPT*, and progranulin, *GRN*) and 3 are rare causes (valosin-containing protein, *VCP*, chromatin modifying protein 2B, *CHMP2B*, and the gene encoding TDP-43, *TARDP*).[2,8] MAPT mutations are associated with tau-positive inclusions pathologically as are the generally sporadic pathologies of corticobasal degeneration, PSP, and Pick disease. *GRN, VCP, TARDP,* and *CHMP2B* mutations are associated with the other major pathologic FTLD type where there are tau-negative inclusions.[1,9] This second subtype can be further subdivided into those with TDP-43-positive pathology, known as FTLD-TDP (of which there are 4 subtypes; this group includes *GRN*, *VCP,* and *TARDP* mutations) and those without, known as FTLD-UPS (including *CHMP2B* mutations). The 5 known genes do not account for all familial cases of FTLD, however, suggesting that there are other disease-causing genes yet to be discovered. This study was designed to look at the heritability of FTLD in each of the different clinical syndromes and to investigate to what extent the known genes account for this heritability. We also looked at the patients with strong family histories of FTLD but without known mutations and the underlying pathologic causes in this group.

METHODS **Sample collection.** Blood was collected for DNA extraction from patients attending the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, Queen Square, London, and also from patients involved in studies of FTLD at the Dementia Research Centre, Institute of Neurology, Queen Square, London. Samples were taken from 225 patients who had been diagnosed by clinical, behavioral, and neuropsychologic assessments with a diagnosis within the FTLD spectrum according to consensus criteria.[3,10-12] Although samples were collected from patients with and without a family history, there is likely to be some ascertainment bias toward familial cases.

Standard protocol approvals, registrations, and patient consents. Ethical approval for the study was obtained from the National Hospital for Neurology and Neurosurgery Local Research Ethics Committee. Written research consent was obtained from all patients participating in the study.

Analysis of family history. All patients were given a modified Goldman score between 1 and 4 as per Goldman et al.,[13,14] where 1 is an autosomal dominant family history of FTLD, MND, CBS, or PSP, defined as the presence of at least 3 affected people in 2 generations with 1 person being a first-degree relative of the other 2, 2 is familial aggregation of 3 of more family members with dementia but not meeting criteria for 1, 3 is 1 other affected family member with dementia (modified to give a

score of 3 only if there is a history of young-onset dementia within the family, i.e., less than 65, and 3.5 if onset above 65), and 4 is no or unknown family history. All patients had had a structured clinical interview which had included a detailed family tree. This had been discussed with the patient and family members (a minimum of 1 other person). The data for this study were ascertained from a review of all of the clinical notes: data were available on 222 of the cases with only 3 patients scoring 4 because of an unknown family history (2 with bvFTD and 1 with FTD-MND).

Genetic analysis. All 225 patients were screened for mutations in *MAPT* and *GRN,* detecting 39 pathogenic mutations. Of the remaining 186 mutation negative patients, sequencing was obtained for *VCP* exons 3, 5, 6, and 10 in 160 patients, *TARDBP* exons 4 and 6 in 179 patients, and *CHMP2B* in 92 patients. We also sequenced exon 15 of the *FUS* gene in 183 patients, which has previously been shown to be causative of motor neuron disease, although currently no mutations have been found in FTLD.[15,16] PCR amplicons were generated using primers at 500 μM in MegaMix Blue PCR cocktail (Microzone). Details of primers and PCR conditions are available on request. Amplicons cleaned with Microclean (Microzone) were sequenced using Applied Biosystems BigDye v1.1 cycle sequence chemistry with 1 μL BigDye, 5 μL BetterBuffer (Microzone), 0.75 μL sequencing primer at 5 pmol/μL, 2.5 ng of cleaned amplicon, and ddH$_2$O to a final volume of 15 μL. Following 25 thermal cycles, sequencing products were precipitated and cleaned used standard EtOH/EDTA methodology and electrophoresed on an ABI 3130xl automated sequencer. Data were analyzed using ABI Seqscape software v2.5. For details of *GRN* and *MAPT* sequencing, see Beck et al., 2008,[14] and Janssen et al., 2002.[17]

RESULTS **Demographic and family history data.** Almost half of the 225 patients had bvFTD as their initial clinical syndrome (44.4%) with the next most common disorders being SemD (16.0%) and PNFA (13.3%). Smaller numbers had CBS or a CBS/PNFA overlap syndrome, PSP or LPA. Average age at onset for the different groups was between 54.8 years (bvFTD) and 62.0 years (PNFA) with a total mean of 57.3 years. In total, 58.2% of the patients were male, with more male patients in each of the groups apart from the CBS and CBS/PNFA overlap groups. A total of 10.2% of patients had an autosomal dominant inheritance (as defined by a modified Goldman score of 1) but the heritability of FTLD was substantially higher (41.8%) when a family history was defined by a modified Goldman score of 1, 2, 3, or 3.5. The bvFTD group had the largest proportion of cases with a family history (58.0% with modified Goldman score 1 to 3.5 and an average modified Goldman score of 2.9) and the least familial of the disorders were FTD-MND (10.0%, 3.8), LPA (20.0%, 3.6), and SemD (22.2%, 3.8) (table 1).

Genetic analysis. Mutations were found in the *MAPT* and *GRN* genes but no mutations were found in the *CHMP2B, VCP*, *TARDBP,* or *FUS* genes. In total, 20 patients (8.9%) had mutations in *MAPT* (15 probands) and 19 patients (8.4%) had mutations in

Table 1 Demographic and family history data for the cohort of 225 patients with frontotemporal lobar degeneration

Initial clinical syndrome	No.	% of total cases	Average AAO	% Male	Modified Goldman score (% of cases)					% of cases with score 1–3.5	Average score
					1	2	3	3.5	4		
bvFTD	100	44.4	54.8	64.0	20.0	17.0	11.0	10.0	42.0	58.0	2.9
FTD-MND	10	4.4	56.7	70.0	0.0	10.0	0.0	0.0	90.0	10.0	3.8
SemD	36	16.0	57.9	52.8	0.0	5.6	5.6	11.1	77.8	22.2	3.8
PNFA	30	13.3	62.0	63.3	0.0	13.3	0.0	16.7	70.0	30.0	3.7
PNFA/CBS	8	3.6	61.3	12.5	12.5	0.0	12.5	12.5	62.5	37.5	3.4
CBS	17	7.6	57.6	41.2	5.9	11.8	17.6	17.6	47.1	52.9	3.3
PSP	9	4.0	58.9	55.6	0.0	33.3	0.0	0.0	66.7	33.3	3.3
LPA	15	6.7	60.7	60.0	6.7	6.7	0.0	6.7	80.0	20.0	3.6
Total	225		57.3	58.2	10.2	13.3	7.6	10.7	58.2	41.8	3.5

AAO = age at onset of symptoms; bvFTD = behavioral variant frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; SemD = semantic dementia; PNFA = progressive nonfluent aphasia; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; LPA = logopenic/phonologic variant of primary progressive aphasia.

GRN (13 probands). Of the *MAPT* mutations, 13 (from 8 families) had an intronic 10 + 16 mutation of which 7 families have previously been described.[17] The other previously described mutations were an intronic 10 + 19 mutation as well as deltaK280, L284R, N296N,[18] S320F, and G389R mutations. A novel MAPT variant was also found, N286N, a synonymous change similar to the N296N which is thought to be pathogenic via its effect on the splicing of exon 10.[18] Most patients presented with bvFTD (although many developed semantic impairment as the disease progressed) apart from the N296N (CBS) and the L284R (PSP) mutations. The *GRN* mutations were 10 C31fs mutations (from 4 families) and 2 385_388delAGTC mutations (from 2 families).[14] Other mutations were 603_603insC, 1494_ 1498delAGTGG, Q300X, L469F, A199V mutations (all previously described in Beck et al., 2008[14]) as well as 1048_1049insG[19] and R493X mutations. Patients were diagnosed with bvFTD (C31fs, 385_388delAGTC, Q300X), PPA (PNFA or LPA: C31fs, L469F, R493X, 603_603insC), or CBS (1048_ 1049insG, A199V, C31fs, 1494_1498delAGTGG) with 2 patients having a PNFA/CBS overlap (C31fs, 1494_1498delAGTGG).

Of the 186 patients without a known mutation, we re-examined the number of cases with a family history and in particular we looked at whether any of the "familial" cases had postmortem confirmation of FTLD pathology (table 2). The majority of these cases (125) had a modified Goldman score of 4 but 4 cases with an autosomal dominant family history (modified Goldman score of 1) were still without a known mutation (all with bvFTD) and in total 61 cases with a modified Goldman score of 1, 2, 3, or 3.5 were not known to have a mutation. We looked particularly at those cases with a score of 1, 2, or 3 (38 in total) as a score of 3.5 may well represent another family member with old-age onset dementia and therefore less likely to be a true familial history of FTLD. Of these 38 cases, 7 had pathologic confirmation of disease (6 bvFTD and 1 FTD-MND). All of these cases had tau-negative FTLD pathology: 1 case with bvFTD was known to have ubiquitin-positive, TDP-43 negative pathology (FTLD-UPS) without intranuclear inclusions similar to the pathology found in the Danish family with a mutation in *CHMP2B* (but in this case without a *CHMP2B* mutation) but the other 6 all had FTLD-TDP (i.e., TDP-43 pathology) with all having type 3 pathology according to consensus criteria.[1,9]

Table 2 Number of cases without mutations stratified according to family history

	Modified Goldman score (n cases)					Total n
	1	2	3	3.5	4	
bvFTD	4	15	7	9	39	74
FTD-MND	0	1	0	0	9	10
SemD	0	2	2	4	27	35
PNFA	0	2	0	5	20	27
PNFA/CBS	0	0	0	1	5	6
CBS	0	1	2	3	8	14
PSP	0	2	0	0	6	8
LPA	0	0	0	1	11	12
Total	4	23	11	23	125	186

bvFTD = behavioral variant frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; SemD = semantic dementia; PNFA = progressive nonfluent aphasia; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; LPA = logopenic/phonologic variant of primary progressive aphasia.

DISCUSSION Our results confirm previous findings that FTLD is a highly heritable degenerative disorder. Heritability varies between the different clinical syndromes, with SemD and LPA having a much lower percentage of cases with a family history compared with bvFTD. SemD is typically a sporadic disease and is associated with type 1 FTLD-TDP[20] although patients with *MAPT* mutations will often develop semantic impairment later in the disease (with behavioral symptoms initially). There are few reports of the associations of LPA with family history although some studies suggest that the majority of cases of LPA actually have Alzheimer-type pathology rather than an FTLD pathology, which would account for the lower rate of reported family history in this group.[4,21] A previous study suggested that FTD-MND was the most heritable of the FTLD syndromes[13] but in our series it was the least heritable, albeit with low numbers in our cohort. Inconsistent results with other series may reflect ethnogeographic clustering of particular causal mutations. Numbers were also low in the PSP group, limiting the ability to interpret these data.

Mutations in *MAPT* and *GRN* are relatively common and have a similar prevalence in our series. However, there is variability in the prevalence geographically across different reported series with *MAPT* mutation frequency between 3% and 14%[22-25] and GRN mutation frequency between 1% and 16%,[26-31] with some series reporting vastly different frequencies within the same country, e.g., 2 studies of FTLD patients in Italy found GRN mutation frequencies of 1.6% and 15.2%.[30,31] A number of recent series have compared the frequency of *MAPT* and *GRN* mutations in FTLD populations[26-29] (table 3): some countries have families with a founder effect causing higher *GRN* mutation prevalence than *MAPT,* e.g., in Belgium.[26] In the United Kingdom, the 10 + 16 *MAPT* mutation is common with a known founder effect[32] which is likely to account for the higher frequency of *MAPT* mutations in some series,[29] although we have also previously shown that patients in our series with the *GRN* C31fs mutation

are part of the same family,[14] which is likely to at least partly account for the similar prevalence of *GRN* and *MAPT* mutations in our series.

We found no mutations in *VCP, CHMP2B,* or *TARDP* consistent with previous series suggesting that these are rare causes of FTLD.[2] It remains possible that causal mutations in these genes are present in unscreened exons of these 3 genes, although our sequencing strategy covered all known mutations in these genes to date. We also found no mutations in *FUS,* suggesting that mutations in this gene are either not causative or are a very rare cause of FTLD.

Taking into account the known mutations, many patients were still found to have a strong family history, suggesting that there are still unknown genes that cause FTLD.[33] One locus (on chromosome 9) is known for patients with a clinical phenotype of FTD-MND[34]; however, this is associated with type 2 FTLD-TDP. Analysis of the pathologic cases within this subgroup suggests that there are at least 2 other groups of patients with a family history without a known mutation: those with FTLD-UPS and those with type 3 FTLD-TDP without a GRN mutation (some of whom have a clinical phenotype of FTD-MND). A number of series have now been reported with FTLD-UPS (ubiquitin-positive, TDP-43 negative) pathology although these have all been reported as sporadic cases.[35,36] The family reported here is pathologically distinct from these patients, lacking the intranuclear inclusions seen in these cases. Although similar pathologically to cases with *CHMP2B* mutations, the single case in our series was negative for mutations in this gene. Studies of type 3 FTLD-TDP suggest that between 30% and 60% of such patients have *GRN* mutations but some patients negative for *GRN* mutations still have a family history.[37,38,39] There are no known loci associated with such patients, suggesting further work needs to be done to clarify the genetic cause in this group as well as patients with familial FTLD-UPS.

DISCLOSURE

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Table 3	Previously reported series comparing frequencies of *MAPT* and *GRN* mutations in a frontotemporal lobar degeneration spectrum population				

Series	Geographic area	No. in series	% MAPT mutations	% GRN mutations
This series	UK	225	8.9	8.4
Cruts et al., 2006[26]	Belgium	103	1.9	10.7
Gass et al., 2006[27]	USA	167	4.4	4.8
Le Ber et al., 2007[28]	France	210	2.9	4.8
Pickering-Brown et al., 2008[29]	UK	223	7.6	5.8

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