Frequency and clinical characteristics of progranulin mutation carriers in the Manchester frontotemporal lobar degeneration cohort: comparison with patients with MAPT and no known mutations

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Two hundred and twenty-three consecutive patients fulfilling clinical diagnostic criteria for frontotemporal lobar degeneration (FTLD), and 259 patients with motor neuron disease (MND), for whom genomic DNA was available, were investigated for the presence of mutations in tau (MAPT) and progranulin (PGRN) genes. All FTLD patients had undergone longitudinal neuropsychological and clinical assessment, and in 44 cases, the diagnosis had been pathologically confirmed at post-mortem. Six different PGRN mutations were found in 13 (6%) patients with FTLD. Four apparently unrelated patients shared exon Q415X 10 stop codon mutation. However, genotyping data revealed all four patients shared common alleles of 15 SNPs from rs708386 to rs5848, defining a 45.8-kb haplotype containing the whole PGRN gene, suggesting they are related. Three patients shared exon 11 R493X stop codon mutation. Four patients shared exon 10 V452WfsX38 frameshift mutation. Two of these patients were siblings, though not apparently related to the other patients who in turn appeared unrelated. One patient had exon 1 C31LfsX34 frameshift mutation, one had exon 4 Q130SfsX130 frameshift mutation and one had exon 10 Q468X stop codon mutation. In addition, two non-synonymous changes were detected: G168S change in exon 5 was found in a single patient, with no family history, who showed a mixed FTLD/MND picture and A324T change in exon 9 was found in two cases; one case of frontotemporal dementia (FTD) with a sister with FTD+MND and the other in a case of progressive non-fluent aphasia (PNFA) without any apparent family history. MAPT mutations were found in 17 (8%) patients. One patient bore exon 10 + 13 splice mutation, and 16 patients bore exon 10 + 16 splice mutation. When PGRN and MAPT mutation carriers were excluded, there were no significant differences in either the allele or genotype frequencies, or haplotype frequencies, between the FTLD cohort as a whole, or for any clinical diagnostic FTLD subgroup, and 286 controls or between MND cases and controls. However, possession of the A allele of SNP rs9897526, in intron 4 of PGRN, delayed mean age at onset by ~4 years. Patients with PGRN and MAPT mutations did not differ significantly from other FTLD cases in terms of gender distribution or total duration of illness. However, a family history of dementia in a first-degree relative was invariably present in MAPT cases, but not always so in PGRN cases. Onset of illness was earlier in MAPT cases compared to PGRN and other FTLD cases. PNFA, combined with limb apraxia was significantly more common in PGRN mutation cases than other FTLD cases. By contrast, the behavioural disorder of FTD combined with semantic impairment was a strong predictor of MAPT mutations. These findings complement recent clinico-pathological findings in suggesting identifiable associations between clinical phenotype and genotype in FTLD.

Keywords: progranulin; tau; MAPT; progressive non-fluent aphasia; apraxia; frontotemporal dementia; genetics
Introduction

Frontotemporal lobar degeneration (FTLD) is a descriptive term that refers to a heterogeneous group of non-Alzheimer forms of dementia with onset of illness usually before 65 years of age arising from the degeneration of the frontal and temporal lobes. Frontotemporal dementia (FTD) is the main syndrome falling under the clinical umbrella of FTLD, and is associated with bilateral atrophy of the frontal and temporal lobes. The related disorders of semantic dementia (SD) and progressive non-fluent aphasia (PNFA) stem from bilateral atrophy of the temporal lobes and the left cerebral hemisphere, respectively (Neary et al., 2005). FTD with motoneuron disease (MND) arises when the behavioural and personality changes of FTD are accompanied by clinical changes of MND (Neary et al., 2005).

At post-mortem, about 45% cases FTLD display a tauopathy in the form of intraneuronal neurofibrillary tangles or Pick bodies. However, a tau-negative, ubiquitin positive histology, exemplified by the presence of neuronal cytoplasmic inclusions (NCI) and/or neuritic changes in cerebral cortex and known as FTLD-U, is probably the most common histological change underlying FTLD (Bergmann et al., 1996; Hodges et al., 2004; Josephs et al., 2004; Lipton et al., 2004; Mott et al., 2005; Taniguchi et al., 2004; Shi et al., 2005; Forman et al., 2006). In some familial FTLD-U cases, neuronal intraneuronal inclusions (NII) of a ‘cat’s eye’ or ‘lentiform’ appearance (Woulfe et al., 2001; Mackenzie and Feldman, 2003) have been described (Rosso et al., 2001; Mackenzie et al., 2006c). Very recently, the major protein component of these ubiquitinated lesions in FTLD has been identified as the TAR DNA-binding protein, TDP-43 (Arai et al., 2006; Neumann et al., 2006; Davidson et al., 2007).

Up to 40% of the individuals with FTLD have similarly affected first-degree relatives consistent with autosomal dominant inheritance (Chow et al., 1999; Rizzu et al., 1999). In some patients, there are mutations in the tau (MAPT) gene (Hutton et al., 1998; see Pickering-Brown, 2007b for review) whereas others bear mutations in the progranulin gene (PGRN) (Baker et al., 2006). Since the initial report (Baker et al., 2006), this latter finding has been widely confirmed (Benussi et al., 2006; Boeve et al., 2006; Cruts et al., 2006; Gass et al., 2006; Huey et al., 2006; Maselli et al., 2006; Mukherjee et al., 2006; Pickering-Brown et al., 2006; Snowden et al., 2006; Behrens et al., 2007; Bronner et al., 2007; Le Ber et al., 2007; Leberenz et al., 2007; Mesulam et al., 2007; Seelaar et al., 2007; Spina et al., 2007). Reported PGRN mutations include missense mutations generating premature stop codons, insertion or deletion mutations resulting in frameshifts or changes within initiation codons precluding transcription. PGRN mutations induce PGRN haploinsufficiency through the creation of a null allele, with any mutant mRNA transcribed being removed by nonsense-mediated decay (NMD) (Baker et al., 2006). Other mutations, in exon 0 leading to nuclear degradation, and mutations that affect the Kosak sequence, preventing translation, are also believed to result in haploinsufficiency (Cruts et al., 2006).

Nevertheless, most reports on PGRN mutations have been based upon single cases or families selected from larger series of patients, or on cases collected from many different sources specifically for genetic linkage studies. Consequently, it is not clear what type of PGRN mutations might be encountered within a given FTLD population drawn from the same geographical area, or how frequent PGRN mutations might be within such an unselected population of cases with FTLD compared with that of patients with MAPT mutation. Furthermore, all FTLD cases with PGRN mutations reported so far have shown FTD, PNFA or CBD clinical phenotype (Benussi et al., 2006; Boeve et al., 2006; Cruts et al., 2006; Gass et al., 2006; Huey et al., 2006; Maselli et al., 2006; Mukherjee et al., 2006; Pickering-Brown et al., 2006; Snowden et al., 2006; Behrens et al., 2007; Bronner et al., 2007; Le Ber et al., 2007; Leberenz et al., 2007; Mesulam et al., 2007; Seelaar et al., 2007; Spina et al., 2007). Hence, it is not known whether PGRN mutations are associated with rarer SD or FTD+MND clinical phenotypes. Moreover, despite showing differing underlying histologies, it is unclear whether cases of FTLD with MAPT or PGRN mutation can be differentiated on the basis of their clinical presentations and progression.

In the present study, we have sequenced PGRN in 223 consecutively accessioned patients with FTLD, noted what type of PGRN mutations are present, and looked to see how frequent these occur in relationship to MAPT mutations. We have also investigated whether there are distinctive clinical and pathological phenotypes that might distinguish bearers of PGRN mutation from those with MAPT mutation, or indeed either of these from patients with FTLD without known mutation. This latter goal is important as the ability to distinguish genetic risk in patients with FTLD will have clinical, patient management and potential therapeutic value in centres where genetic analysis is not always practical or possible. Finally, FTD can be associated with clinical MND, and TDP-43 pathology is available to assist with this discrimination. We also report on an FTD case that has recently been found to have a novel PGRN mutation.
a feature of around 65% of FTLD and cases of MND where SOD-1 mutation is absent (Arai et al., 2006; Neumann et al., 2006; Davidson et al., 2007; Tan et al., 2007) suggesting a possible aetiological link between these two conditions. Therefore, we have performed a linkage disequilibrium study of the PGRN locus in FTLD patients without either PGRN or MAPT mutations, and in patients with MND, in order to assess whether any common variants of this locus increase the risk of developing either or both of these conditions.

Material and Methods

Patients

The study group comprised 223 consecutive patients, 119 men and 104 women, referred to the Cerebral Function Unit (CFU), University of Manchester, who fulfilled clinical diagnostic criteria for FTLD (Groups, 1994; Neary et al., 1998), and for whom genomic DNA was available. All patients had undergone longitudinal neuropsychological and clinical assessments within the Cerebral Function Unit, and in 44 cases, the diagnosis had been pathologically confirmed at post-mortem. Patients’ mean age at onset of symptoms was 58.9 years. A positive family history of dementia in a first-degree relative was recorded in 40% of cases.

Forty-three per cent of patients had presented with a prominent behavioural disorder and disexecutive syndrome in keeping with FTD (Neary et al., 1998), 13% of patients showed a circumscribed semantic disorder, consistent with SD and 8% a circumscribed expressive language disorder consistent with PNFA. Some patients exhibited at presentation a mixed picture, in 16% the prominent behavioural changes of FTD being combined with semantic impairment, and in 4% with expressive non-fluent aphasia. In 14% of cases, FTLD syndromes (10% FTD, 3% FTD+SD and 1% PNFA) were associated with physical signs of MND. Two per cent of cases presented initially with apraxia (PAX).

Blood samples were also available from an unselected sample of 259 patients with MND (mean age at onset 57.8 years, range 28–79 years), diagnosed in a specialist neurological motoneuron disease clinic. The majority of patients met El Escorial criteria for clinically definite or probable amyotrophic lateral sclerosis (ALS) (Brooks et al., 2000). Sixty-seven of the MND cases have been used in a similar much smaller study of PGRN (Xiao et al., 2007). Controls comprised 286 mentally normal people [mean age 54.2 years at time of sampling (SD 12.2 years), range 26–81 years] collected from the Manchester and Birmingham regions of the UK.

All samples were recruited with Ethical Committee approval, and provided informed consent. All samples were of UK origin.

Genetic methods

PGRN sequencing

For all 223 patients with FTLD, exons 1 to 13 of the PGRN were amplified as previously described (Baker et al., 2006). Sequence analysis was performed using an ABI3730.

Genotyping analysis

Thirty-eight SNPs covering 174.6 kb (position 39683019 to 39857655, Supplementary Table 1) encompassing the whole PGRN and flanking area were chosen from phase II data from the International HapMap Project. SNPs were genotyped using the Sequenom MassArray genotyping technology according to manufacturer’s instructions. SpectroTYPER software was used to automatically assign the genotype calls.

Statistical analysis

Haplotype block structure was examined using haploview (http://www.broad.mit.edu/mpg/haploview). For comparison with this study, PGRN data (chromosome 17 positions 39683019 to 39857655) from the HapMap project (http://www.hapmap.org/) was used. Haploview was used to define haplotype blocks using the confidence intervals option, where 95% confidence bounds on D’ (prime) are generated. To reconstruct haplotypes from genotype data, Phase version 2.1 was used (Stephens and Donnelly, 2003), using 10 000 iterations and a burn in of 10 000. Stata (v9) was used to estimate OR and 95% CI for haplotypes using unconditional logistic regression, the most common haplotype being used as the baseline for analysis. CLUMP (Sham and Curtis, 1995) was used to assess the $\chi^2$ significance of the haplotypes between groups. For the univariate analyses, the study had 93.4% power ($P=0.05$) to detect an odds ratio of 0.5 when the exposure level was 40% in the control population and a power of 57% ($P=0.05$) to detect an odds ratio of 1.5.

Pathological methods

Brains from the 44 deceased patients had been fixed in 10% buffered formalin for a period between 1 and 3 months. Blocks of tissue were cut from frontal (Brodmann areas 8/9), and temporal (Brodmann areas 21/22) cortex and hippocampus (at the level of the geniculate bodies) from all patients, and from brainstem (at levels of trigeminal and facial motor nerve nuclei) and medulla oblongata (at level of hypoglossal motor nerve nucleus and including the inferior and superior olivary nuclei) and spinal cord (at cervical, thoracic and lumbar levels) where these were available. Tissue blocks were processed routinely into paraffin wax and sections were cut at a thickness of 5 μm.

Sections of frontal and temporal cortex were immunostained for ubiquitin using an automated staining procedure using a polyclonal anti-ubiquitin antibody (Dako, Glostrup, Denmark, 1:500) (see Mackenzie et al., 2006d, for details) and manually for TDP-43 using a commercially available polyclonal antibody (10782-1-AP, Protein Tech Inc, Chicago, IL, USA) at a dilution of 1: 1000 (see Davidson et al., 2007). Sections of brainstem and spinal cord (where available) were similarly immunostained for TDP-43, and manually for ubiquitin using the same (Dako) polyclonal anti-ubiquitin antibody (1:500) using a standard ABC protocol. Tau immunostaining had previously been performed using AT8 antibody (Shi et al., 2005; Shiarli et al., 2006).

Results

Genetic analysis

PGRN mutations were found in 13 out of 223 (6%) patients with FTLD (Table 1). Eight PGRN mutations were identified from blood samples (see Patients #1–8), and five from brain tissue (see Patients #9–13). Six different PGRN mutations were present. Two patients (Patients #5 and 6) shared exon 11 R493X stop codon mutation. In the case of
Patient #14, no DNA was available for analysis but this individual was the sibling of Patient #6, and shared a similar illness. Moreover, DNA analysis of another sibling, who was not investigated at CFU, but said to have developed behavioural changes, showed the same mutation as Patient #6. Patient #14 is therefore presumed to bear the same mutation as her two siblings. These three patients (Patients #6, 7 and 14) were not apparently related to Patient #5. Four also apparently unrelated patients (Patients #1–4) shared exon Q415X 10 stop codon mutation. However, inspection of genotyping data revealed all four patients shared common alleles of 15 SNPs from rs708386 to rs5848, defining a 45.8 kb haplotype that contains the whole PGRN gene, and suggesting these four patients are indeed related. In none of these four patients was there a known history of dementia. Four patients (Patients #7–10) shared exon 10 V452WfsX38 frameshift mutation. Two of these patients (Patients #7 and 8) were siblings, though not apparently related to Patients #9 and 10 who in turn appeared unrelated. Inspection of genotyping data revealed these patients share alleles of 37 SNPs (rs1476512–rs11079133) including PGRN and surrounding locus defining a common haplotype of 172 kb. Patient #11 had exon 1 C31LfsX34 frameshift mutation, Patient #12 had exon 4 Q130SfsX130 frameshift mutation and Patient #13 had exon 10 Q468X stop codon mutation. Patients #12 and 13 have been previously reported (Baker et al., 2006; Snowden et al., 2006).

**PGRN association analysis**

PGRN association analysis was performed on the 192 FTLD patients without either PGRN or MAPT mutation, and on all 259 MND patients and all 286 control subjects. All PGRN allele and genotype frequencies matched data on dbSNP or the HapMap data for Caucasian populations, and were in Hardy–Weinberg equilibrium (data not shown). Analysis using logistic regression demonstrated no significant differences in either the allele or genotype frequencies between the FTLD cohort as a whole (when the PGRN or MAPT mutation carriers were excluded), or for any clinical diagnostic FTLD subgroup and controls (Supplementary Table 1), or when the 192 FTLD cases were stratified into those with or without previous family history (data not shown).

**Table 1 Clinical phenotypes, demographic and genetic details on 14 patients with FTLD with PGRN mutations and 17 with MAPT mutations**

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shown). However, linear regression analysis identified that the A allele of SNP rs9897526 significantly delayed mean age at onset by ~4 years [GG genotype, n = 142, mean age at onset 58.71 (range 23–79); GA genotype, n = 35, mean age at onset 62.42 (range 42–83); AA genotype, n = 3, mean age at onset 54.25; Prob >F = 0.0493]. Using CEPH HapMap data the haplotype block structure for PGRN locus was defined using the confidence intervals method of Gabriel et al. (2002). Comparison of the haplotype data generated identified four haplotype blocks, with blocks 3 and 4 containing all of PGRN. Eight haplotypes was observed in block 3 describing 91.75% of the genetic information, whereas five haplotypes were observed in block 4 representing 97.6% of the information. No statistically significant difference was observed in the frequency of any haplotype, either for all 192 FTLD patients as a whole (Supplementary Table 2), or when stratified according to previous family history or clinical diagnostic FTLD subgroup, when compared with control data (Supplementary Table 2). The data was likewise negative when the analysis was restricted to those FTLD cases with autopsy confirmation: this latter analysis however lacked statistical power given the small number of cases. No effect was noted for age and sex for any of the variants or haplotypes analysed.

Non-synonymous changes in PGRN

In addition to the PGRN mutations described above, two non-synonymous changes were also detected. A G168S change in exon 5 was found in a single patient, with no family history, who showed a mixed FTLD/MND picture. Also, A324T change in exon 9 was found in two cases; one case of FTD with a sister with FTD+MND and the other in a case of PNFA without any apparent family history.

MAPT analysis in FTLD

MAPT mutations were found in 17 out of 223 (8%) patients (Patients #15–31) (Table 1). Eleven MAPT mutations were identified from blood samples (Patients #15–25, Table 1), and six from brain tissue (Patients #26–31, Table 1). One patient (Patient #15) bore exon 10+13 splice mutation, and 16 patients (Patients #16–31) bore exon 10+16 splice mutation. Fourteen of these patients (Patients #15–26, 23–30) have been reported previously (Pickering-Brown et al., 2002).

MAPT haplotypes in the PGRN mutation cases (where performed) were H1H1, H1H2 and 2 H2H2 (H1 frequency = 59%), whereas all 17 patients with MAPT mutations had H1H1 haplotype. The APOE e4 allele frequency in the PGRN mutation cases was 18.2% (8 e3/e3, 2 e3/e4, 1 e4/e4) and was 20.6% (1 e2/e3, 9 e3/e3, 7 e3/e4) in the MAPT mutation cases. Neither H1 haplotype frequency nor APOE e4 allele frequency differed between PGRN and MAPT mutationbearers.

Control and MND cases

Analysis of the 259 MND cases also failed to demonstrate any significant association with PGRN locus either at the genotype or haplotype level (Supplementary Table 3) and there was no apparent effect of age or sex. Unlike that observed for FTLD rs9897526 had no effect on age at onset [GG genotype, n = 106, mean age at onset 58.51 (range 28–79); GA genotype, n = 35, mean age at onset 57.71 (range 36–70); AA genotype n = 0; P = 0.563].

Clinico-molecular relationships

Demographic characteristics

Patients with PGRN and MAPT mutations did not differ significantly from other FTLD cases in terms of gender distribution. The male: female frequencies for PGRN cases were 5: 9, for MAPT cases 10:7 and for other FTLD cases 104: 88. A family history of dementia in a first-degree relative was present in 71% of PGRN cases, 100% of MAPT cases and 39% of other FTLD cases. Paired-comparisons showed that the lower familial incidence in PGRN compared to MAPT cases was statistically significant (Fisher’s exact test, P = 0.04), as was the higher incidence in PGRN and MAPT cases compared to other FTLD cases (Fisher’s exact test P = 0.006 and P < 0.001, respectively). Onset of illness was earlier in MAPT cases [mean 53(6) years] compared to PGRN [mean 59(5) years] (t = 3.1, P = 0.004) and other FTLD cases [mean 59(9), t = 2.5, P = 0.01]. Onset age in PGRN cases did not differ significantly from that in other FTLD cases. Total duration of illness was comparable across all groups [mean 9(4), 8(4) and 7(4) years for PGRN, MAPT and non-mutation bearers, respectively].

Clinical phenotypes

In PGRN cases, the clinical presentation took two main forms (Fig. 1). Approximately half of the patients, i.e. 8/14 (57%) exhibited a severe, yet circumscribed frontal lobe syndrome, consistent with typical FTD. In these patients, behavioural changes of apathy and loss of volition predominated and became increasingly marked over the course of the disease. Speech output became progressively attenuated, and there were frontal features of echolalia, verbal stereotypes and perseverations, prior to the onset of mutism. Performance on cognitive assessment was characterized by economy of effort, frequent ‘don’t know’ responses, concreteness and perseveration and severe impairments on executive tasks. Despite the reduction in speech, at no time during the course of the illness was there evidence of frank aphasia, as defined by the presence of grammatical, phonological or semantic errors. Neuroimaging showed bilateral atrophy affecting predominantly the frontal and to a lesser extent anterior temporal lobes. The clinical profile is exemplified by Case #13, described previously (Snowden et al., 2006) as the proband of Family F53. The frequency of this typical FTD profile
found in PGRN cases was not significantly different from that in other cases of FTLD.

In 5/14 cases (36%), the presentation was of an expressive language disorder, consistent with PNFA. The prominent feature was anomia, the word retrieval difficulties becoming sufficiently pronounced to give rise to a non-fluent quality to patients’ utterances. Nevertheless, there were no problems in articulation, and phonological errors were rare or absent, suggesting problems arising at the level of accessing word forms rather than in motor production. One patient (Patient #11), despite being unable to name objects, could spell out those same object names (Snowden and Neary, 2003), a finding interpreted as evidence of a selective impairment in access to the phonological form of the word. In four anomic patients, a gestural PAX was documented during the disease course. Neuroimaging showed severe asymmetric atrophy involving perisylvian regions of the left hemisphere.

One of the 14 (7%) PGRN cases differed from these two main profiles. This patient, who was the brother of Patient #7, presented with an asymmetric, left-sided limb PAX and parkinsonism, suggestive of a diagnosis of corticobasal degeneration (CBD). He too developed problems in language expression, with impaired word retrieval, although these were subsidiary to his profound PAX. Imaging indicated asymmetric atrophy affecting the right hemisphere more than the left. This patient alone displayed akinsiæsia and rigidity of the limbs at presentation. In all other PGRN patients neurological examination was normal at referral. Limb rigidity, generally of mild degree, emerged over the disease course. No patient showed clinical signs of MND. PGRN cases presenting with progressive aphasial/ PAX had a later onset than those presenting with a frontal behavioural syndrome ($t = 3.1$, $P = 0.01$).

Of the 17 MAPT cases, all exhibited prominent alterations in personality and social conduct, consistent with FTD (Fig. 1). In Patient #15, who, uniquely in the series, after an exon 10+13 mutation the behavioural change took the form of loss of volition, apathy, and inertia. In patients with exon 10+16 mutations, by contrast, the prevailing characteristic was of a fatuous affect, purposeless overactivity, inattentiveness and distractibility, disinhibition and inappropriate behaviours that violated social mores. Apathy emerged only in the later stages of disease. Similarly, parkinsonian signs typically emerged as a late feature. Only two patients showed akinsiæsia and rigidity of the limbs at initial presentation. No patient showed clinical signs of MND. All patients showed on neuropsychological assessment evidence of a dysexecutive syndrome, with frank ‘frontal’ features of concreteness and response perseveration. Frontal features were also present in patients’ language: echolalia, perseveration and stereotypies. In addition, the majority exhibited evidence of semantic disorder, evidenced by the presence of semantic errors in naming, impaired word comprehension and impaired recognition of famous faces and names. In no MAPT case were phonological errors recorded in their conversational speech or on formal neuropsychological assessment. Thus, the prevailing profile in patients with MAPT mutations was of a dominant behavioural disorder indicative of frontal lobe dysfunction, combined with semantic impairment. Individual cases histories have been described elsewhere (Pickering-Brown et al., 2002).

Figure 1 shows the distribution of clinical presentations in PGRN, MAPT and other FTLD cases. A clinical presentation of PNFA was significantly more common in PGRN cases than in both MAPT cases (Fisher’s Exact test, $P = 0.01$) and other FTLD cases ($P = 0.005$). A logistic regression analysis showed that the presence of PNFA significantly increased the odds of having a PGRN mutation [Exp(B) 8.0 CI 2.3–27.3]. In contrast, a mixed picture of FTD combined with semantic impairment increased the odds of MAPT mutation [Exp(B)26.6 CI 8–89]. In cases without PGRN or MAPT mutations, the frequency of clinical phenotypes was largely similar in familial and sporadic cases (Fig. 1). The only statistically significant difference was a higher frequency of pure SD in the sporadic group (Fisher’s exact test, $P = 0.03$).

Pathological phenotypes

As we (Baker et al., 2006; Pickering-Brown et al., 2006; Snowden et al., 2006) and others (for example, Cruts et al., 2006; Mackenzie et al., 2006b) have described elsewhere, all six autopsied patients with PGRN mutations displayed a similar histological phenotype, irrespective of the precise mutation present. This was characterized by a moderate number to numerous ubiquitin-immunoreactive neurites,
and NCI within small neurons, in layer II of the frontal and temporal cortex: NII were present in all six patients, though these were never numerous (<12 per section). Such a pattern of ubiquitin pathology has been termed by us, FTLD-U type 1 (Mackenzie et al., 2006d), or by others (Sampathu et al., 2006) as FTLD-U type 3. Granular ubiquitin-immunoreactive inclusions were variably present within granule cells of the dentate gyrus of the hippocampus. Again, as we have previously described (Davidson et al., 2007), TDP-43 immunohistochemistry revealed similar pathological structures within the cerebral cortex and hippocampus as ubiquitin immunohistochemistry. No tau-immunoreactive neurons or glial cells were present in any cerebral cortical region. Within the brainstem, skein-like, spicular or rounded, ubiquitinated, TDP-43 immunoreactive NCI were present in neurons of the inferior olives in all PGRN mutation cases, though no such inclusions were seen in motoneurons of trigeminal or hypoglossal cranial nerve nuclei, or in anterior horn cells of the spinal cord, where these regions were available for examination.

As we (Pickering-Brown et al., 2002) and others (Janssen et al., 2002) have reported previously, all seven patients with MAPT exon 10 + 16 mutation, and the single patient with MAPT exon 10 + 13 mutation, showed identical pathology with tau-immunoreactive neurons within the grey matter, and tau-immunoreactive glial cells (probably oligodendroglia) within the white matter, of the cerebral cortex (data not shown). Although some of the more NFT-like tau deposits within neurons of the cerebral cortex were ubiquitinated, none of these were TDP-43 immunoreactive, nor were glial cell tangles reactive to TDP-43 antibody (data not shown).

Twenty-six patients in the series, without PGRN or MAPT mutations, showed FTLD-U or tau pathology at autopsy. Their clinical phenotype is compared with that of the PGRN and MAPT cases in Table 2. PNFA was more common in PGRN mutation cases than in FTLD-U cases with no PGRN mutation (Fisher’s exact test, $P = 0.05$). FTD combined with semantic impairment predominated in MAPT mutation cases but was absent in cases with tauopathy but no MAPT mutation.

### Discussion

In the present study, sequencing of PGRN in 223 consecutive patients with FTLD revealed the presence of 13 mutations, or 14 mutations if a single affected sibling of two other affected siblings with proven PGRN mutation is included. The prevalence rate in our series was 5.8% of all FTLD cases and 17% of familial FTLD. These figures are largely consistent with other reports. An overall prevalence rate of ~5% was reported by Gass et al. (2006) and Le Ber et al. (2007), accounting for 23% of familial cases in the cohort of Gass et al. and 12.8% in that of Le Ber et al.

In our series, six separate PGRN mutations were identified, two of these mutations (exon 4 Q130SfsX124 mutation in Patient #12 and exon 10 Q468X mutation in Patient #13) having been reported previously by us (Baker et al., 2006). The exon 1 C31LfsX34 and exon 11 R493X mutations have been reported previously in other populations by both ourselves (Baker et al., 2006) and others (Huey et al., 2006; Spina et al., 2007). Haplotypal analysis of microsatellite markers covering the PGRN locus demonstrates that the Manchester cases with the C31LfsX34 and Q130SfsX124 mutations shared the same haplotype as the UBC-17 and UBC-15 families, respectively (data not shown) suggesting common founders. This is not unexpected as UBC-17 is known to be of English origin. Neither the exon 10 Q415X nor V452WfsX38 mutations have been reported previously, though the clinical and pathological (where known) phenotypes of these patients fit with previously reported patients with PGRN mutation. We also identified two non-synonymous changes in PGRN in three patients. The A342T mutation has been reported by others (Gass et al., 2006). While this particular variant has not been found in controls, its exact relationship to disease is unclear. Many of the non-synonymous changes identified in PGRN, that do not lead to null alleles, have been found in controls or have been shown not to segregate with disease in family-based analysis (Gass et al., 2006). Nevertheless, it is possible that this variant and the G168S variants are pathogenic via a novel mechanism (van der Zee et al., 2007). It is noteworthy in this regard that one of the three patients showed clinical signs of MND, whereas another had a family history of FTLD/MND. MND was notably absent in all patients with established PGRN and MAPT mutations.

Association analysis using SNPs covering the PGRN locus failed to demonstrate any effect on disease risk either at the genotype or haplotype level. This argues that, while null mutations of PGRN are pathogenic, common variants (polymorphisms) in this gene do not contribute greatly to an individual’s chance of developing FTLD, or indeed MND alone. While it clear that common variants (polymorphisms) in some genes can increase disease risk,
e.g. MAPT H1 and PSP (Baker et al., 1999), this is not always so. A mutation in CHMP2B causes FTLD in a single family from Denmark (Skibinski et al., 2005), yet common variants of this gene do not increase risk of FTLD (Rizzu et al., 2006; Schumacher et al., 2007). Furthermore, we have recently shown that variants in the TDP-43 gene, the major pathological protein product of FTLD, also do not increase disease risk (Rollinson et al., 2007). Nevertheless, we did observe an effect on age at onset with SNP rs9897526. This polymorphism has also been reported to have the same effect in FTLD patients with the R493X PGRN mutation (Rademakers et al., 2007). Presumably, this variant has a role to play in controlling alternative splicing or expression levels but functional investigations are required to fully elucidate its actions. However, no effect on age at onset was seen for MND, which further supports the concept that PGRN has little contribution to the aetiology of this disease.

Within the same cohort of patients we have identified MAPT mutations in 17 individuals, yielding a prevalence of 8% of all FTLD cases and 21% of familial cases. The overall prevalence is somewhat higher than the figure of 5.9% in all cases, but 10.5% in just familial cases, reported by (Pookraj et al., 2001) and 1.2% by (Huey et al., 2006). The frequency of mutations in our cohort may be inflated by the likelihood of a common founder for MAPT exon 10 + 16 mutation being located within nearby North Wales region of UK (Pickering-Brown et al., 2004), with residents of that region falling into the catchment area of our Centre. A similar inflated frequency of PGRN mutations has been described in a Belgian FTLD cohort where ~7% of cases result from a founder family (Cruts et al., 2006; van der Zee et al., 2006). Present data suggest therefore that PGRN mutations are no greater a cause of FTLD than MAPT mutations, with both collectively explaining well under half of all cases with apparent autosomal dominant inheritance of FTLD. Such data suggest other genetic loci for inherited FTLD. It is possible that many of the remaining familial cases could be accounted for by unidentified gene on chromosome 9p (Morita et al., 2006; Vance et al., 2006).

In all instances, FTLD patients with PGRN mutations displayed a similar tau-negative histological picture (termed type 1 histology by Mackenzie et al., 2006d) in both ubiquitin- and TDP-43-immunohistochemistry. Apart from the presence of numerous ubiquitin- and TDP-43-immunoreactive neurites and NCI within the cerebral cortex, all cases displayed lentiform or ‘cat’s eye’ NII. Indeed, to date, all reported cases with PGRN mutations where brain examination has been possible have shown this particular pathological feature, leading some to argue that the presence of such NII might be pathognomonic. However, within the present series, we observed eight cases with identical (to known PGRN mutation cases) ubiquitin/TDP-43 type 1 histology (including the presence of NII) where no PGRN mutation was present, and in six of these a family history consistent with autosomal dominance was present.

Such data suggest either that there may be other changes within PGRN that have not been detected so far, or that there are other routes to producing this particular histology that do not involve PGRN mutations, but could likewise induce a PGRN protein insufficiency state. Leverenz and colleagues (2007) reported tau and alpha-synuclein pathology in a family with a PGRN mutation (c.709 -2A4G) thought to affect splicing of exon 7, leading to reduced levels of PGRN message. This is similar to a FTLD family reported by Wilhelmsen that also had tau and alpha-synuclein pathology. However, the linkage region in this latter family was distal to the PGRN locus excluding this gene as a cause of disease (Wilhelmsen et al., 2004). Despite these observations, tau and/or alpha-synuclein positive neuropathological structures were not found in any of our present patients, and are not common, if present at all, in other cohorts (Mackenzie et al., 2006b; Josephs et al., 2007; Pickering-Brown, 2007a).

The R493X mutation appears to be the most common PGRN mutation associated with FTLD, with numerous bearers of this particular mutation having been reported in British, Australian, American and Canadian families (Huey et al., 2006; Pickering-Brown et al., 2006; Spina et al., 2007). Recent work has demonstrated these represent a single pedigree that likely originated in England (Rademakers et al., 2007) and spread through British emigration akin to the MAPT exon 10 + 16 mutation as we have described (Pickering-Brown et al., 2004). In the present study, we identified four patients with V452WfsX38 and 3 with Q415X mutations. Both of these are novel mutations, and like the previously reported (Baker et al., 2006) C130SfsX124 (Patient #12) and Q468X (Patient #11) mutations appear confined to British patients.

The Q415X mutation is notable in that none of the four mutation bearers had demonstrable family history of FTLD (or dementia). This is in stark contrast to the other PGRN mutations where all carriers had clear autosomal dominant inheritance of disease. Such observations might suggest Q415X is a relatively rare, though benign, polymorphism chancing to occur in these four patients with otherwise sporadic FTLD. There are arguments against this. Firstly, like many of the other PGRN mutations, the Q415X mutation introduces a premature stop codon, and there is no reason why this change should not lead into PGRN haploinsufficiency, similar to other (nearby) mutations e.g. R418X. Secondly, we were unable here to show the presence of this genetic variation within 286 control subjects, or 259 subjects with MND, and this particular change has not been found in any control subject within any other studies. Finally, haplotype analysis suggests these four patients are related and are part of a larger family. Assuming R415X mutation to be pathogenic, the lack of previous family history in all four patients raises issues of incomplete penetrance. The presence of PGRN mutations in apparently sporadic cases has also been reported by others (Le Ber et al., 2007). The reason for this apparent incomplete
penetrance in certain cases remains to be explained, but likely results from other genetic (e.g. variants that compensatorily upregulate the expression of the normal PGRN allele and negate the effects of the mutation in some carriers) or environmental factors.

The clinical phenotype associated with present PGRN mutations was either of the prototypical behavioural disorder of FTD, or of a non-fluent anomic aphasia, consistent with PNFA (see also Snowden et al., 2006). No patient was noted to display neuropsychological changes reminiscent of SD. Indeed, the ubiquitin histological changes of SD differ markedly from those seen here, with SD patients demonstrating a neurite predominant pattern on ubiquitin/TDP-43 immunohistochemistry that we (Mackenzie et al., 2006a) have termed FTLD-U type 2 (type 1 in Sampathu et al., 2006). Moreover, no PGRN mutation carriers displayed either clinical or histopathological features of MND, and patients with FTD+MND again demonstrate a separate and distinctive histological phenotype on ubiquitin/TDP-43 immunohistochemistry (FTLD-U type 3; Mackenzie et al., 2006a) and type 2 in (Sampathu et al., 2006). Such observations suggest patients with SD or FTD+MND clinical syndromes are unlikely to bear PGRN mutations, and despite sharing a basic ubiquitin/TDP-43 histopathology with bearers of PGRN mutations, these are sufficiently different in morphological characteristics as to suggest separate underlying pathogenetic mechanisms. Such a conclusion is supported by the lack of PGRN mutations, or association with common polymorphisms in PGRN, in patients with clinical MND

Although bearers of PGRN and MAPT mutations all broadly fell under the clinical umbrella of FTLD there were notable differences in neuropsychological expression. In PGRN cases presenting with behavioural change, the ‘frontal lobe’ syndrome was relatively pure, whereas in MAPT cases it was commonly accompanied by semantic deficits. In PGRN cases, the dominant behavioural symptom was apathy, whereas in MAPT cases it was social disinhibition. Most strikingly, the language disorder in PGRN cases took the form of a non-fluent anomic aphasia (PNFA), accompanied by gestural PAX and associated with asymmetric atrophy involving perisylvian regions of the left hemisphere. This profile was never seen in association with MAPT mutations. By contrast, in MAPT cases the language disorder was characterized by semantic loss, and was associated with bilateral atrophy of the temporal (as well as frontal) lobes.

Differences were not confined to those between PGRN and MAPT cases. The PNFA profile was more common in PGRN mutation cases than in cases with no known PGRN mutation, including those with established FTLD-U pathology. The mixed FTD/SD picture occurred with significantly higher frequency in MAPT mutation cases than in cases with no known mutation, including those with established tau pathology. In cases without PGRN or MAPT mutations, the frequency of clinical phenotypes was largely similar in familial and sporadic cases, suggesting that a positive family history per se does not explain the high frequency respectively of PNFA in PGRN cases and mixed FTD/SD in MAPT cases.

There is inevitably a need for caution in drawing strong conclusions about clinical phenotypic differences. The cohort of patients with these mutations is small. Moreover, the MAPT cases in this series are dominated by patients with exon 10+16 mutations, which may not be representative of MAPT mutation cases as a whole. Indeed, whereas the dominant behavioural change in our exon 10+16 cases was disinhibition, that of the single case with an exon 10+13 mutation was apathy, despite both mutations having similar molecular effects. In the literature, the status of semantic functioning in patients with MAPT mutations has not been systematically reported, so that it is not clear whether other cohorts of MAPT cases share a common clinical phenotype, as represented here.

Nevertheless, a notable feature of studies of PGRN mutations is the relatively high frequency with which expressive language impairment is reported (Gass et al., 2006; Snowden et al., 2006; Davion et al., 2007; Josephs et al., 2007; Rademakers et al., 2007). Moreover, consistent with our own findings, an association has also previously been observed between PAX and PGRN mutations (Le Ber et al., 2007; Spina et al., 2007). Such converging findings, together with the highly significant phenotypic differences demonstrated between our PGRN, MAPT and non-mutation cases, suggest that clinical phenotypic variation within FTLD is not arbitrary. There is growing evidence of a predictable relationship between clinical phenotype and underlying histopathology (Snowden et al., 2007). The present results suggest that there may also be identifiable relationships between genetic mutations and clinical expression.

### Supplementary material

Supplementary material is available at *Brain* online.

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