LETTER TO THE EDITOR

Mutations in progranulin explain atypical phenotypes with variants in MAPT

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Mutations in presenilin-1 (PSEN1) cause autosomal dominant Alzheimer's disease and mutations in MAPT cause the familial tauopathy Frontotemporal dementia linked to chromosome 17 (FTDP-17). However, there have been reports of mutations in PSEN1 and MAPT associated with cases of FTD with ubiquitin-positive tau-negative inclusions. Here, we demonstrate that the MAPT variants are almost certainly rare benign polymorphisms as all of these cases harbour mutations in Progranulin (PGRN). Mutations in PGRN were recently shown to cause ubiquitin-positive FTDP-17.

Keywords: frontotemporal dementia; FTLD-U; MAPT; Progranulin

Abbreviations: FTLD = frontotemporal lobar degeneration; NCI = neuronal cytoplasmic inclusions; NII = neuronal intranuclear inclusions; PGRN = progranulin; PSEN1 = presenilin-1; ub-ir = ubiquitin-immunoreactive

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Frontotemporal lobar degeneration (FTLD) is the second most common form of primary degenerative dementia after Alzheimer’s disease (Neary et al., 1998). FTLD is thought to represent up to 20% of cases of presenile dementia. Significantly, a large proportion of FTLD patients (35–50%) have a family history of dementia suggesting a large genetic contribution to the aetiology of this disease (Neary et al., 1998). There have been seven chromosomal loci for FTLD identified to date on chromosomes 3, 9p (two loci), 9q, 17q21 (two loci) and 17q24 with only four genes (MAPT, VCP, CHMP2b and PGRN) identified to date.

Approximately 15–20% of familial FTLD result from mutations in the MAPT gene on chromosome 17q21, which encodes the microtubule associated protein tau (Hutton et al., 1998). There have now been over 35 MAPT mutations reported in exons 1, 9, 10, 11, 12 and 13 in families worldwide. At autopsy, almost all of the reported cases with MAPT mutations have intraneuronal hyperphosphorylated tau based neuropathology and glial cell tau inclusions are observed in some families (Reed et al., 2001).

Very recently we reported that mutations in a second gene on chromosome 17q21, called Progranulin (PGRN), cause autosomal dominant FTLD in a series of families that had previously been shown to lack mutations in MAPT (Baker et al., 2006; Cruts et al., 2006). Moreover, pathologically these families display tau-negative, ubiquitin-immunoreactive (ub-ir) neuronal cytoplasmic inclusions (NCI) and characteristic lentiform ub-ir neuronal intranuclear inclusions (NII) within affected regions of cerebral cortex and hippocampus. All PGRN mutations identified lead to the creation of null alleles with the majority introducing premature termination codons that invoke nonsense mediated RNA decay. This suggests that haploinsufficiency is the likely pathogenic mechanism in these cases.

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Letter to the Editor

There have been reports of two mutations in MAPT and a mutation in presenilin-1 (PSEN1) with clinical diagnoses of frontotemporal dementia (FTD) in which autopsies have revealed unexpectedly tau-negative pathology. This is in marked contrast to the tauopathy and Alzheimer’s disease-type plaque and tangle neuropathologies normally associated with mutations in MAPT and PSEN1, respectively. These findings seemed to imply that specific mutations in these genes might result in a somewhat different pathogenic mechanism leading to alternative pathologies.

We have recently demonstrated that a variation at codon 352 of PSEN1 (PSEN1ins352) in a patient with clinical FTD (Amtul et al., 2002). Other members of this family were unavailable to demonstrate segregation. This case has recently come to autopsy and interestingly this revealed ub-ir NCI and NII pathology. Subsequent sequence analysis of PGRN in this case revealed PGRN IVS1 + 1G > A splice donor site mutation in intron 1 (Fig. 1) (Boeve et al., 2006).

We previously reported a MAPT IVS10 + 29 variant that segregated with disease in a small Australian FTD family with a maximum LOD score of 1.02 and tau-negative neuropathology (Stanford et al., 2003). Assays of MAPT exon 10 alternative splicing suggested that this variant caused increased production of tau protein isoforms with three microtubule binding repeats (3R tau) (Stanford et al., 2003). However, the MAPT IVS10 + 29 mutation was also found at low frequency in controls (D’Souza et al., 1999; Stanford et al., 2003) questioning the pathogenic nature of the variant, although the possibility remained that it was a genetic risk factor for FTLD. We have also reported a tau-negative neuropathology in a British individual with a A239T mutation in MAPT (Pickering-Brown et al., 2002). This mutation was absent in over 900 control individuals, however, the lack of other family members precluded segregation analysis of this mutation. In light of the aforementioned PS-1/PGRN finding, we then questioned whether cases with variants in MAPT associated with tau-negative FTD also had ub-ir NCI and NII pathology. Re-evaluation of these two MAPT + 29 and A239T cases, using a sensitive automated ubiquitin immunostaining protocol shown to detect ub-ir pathology in other FTLD patients though to display a tau- and ubiquitin-negative histology (known as dementia lacking distinctive histology) (Mackenzie et al., 2006), indeed revealed NCI and NII to be present in both instances (Fig. 1A and B).

Given the proximity of PGRN and MAPT (1.7 Mb) on chromosome 17 it is possible that these rare variants in MAPT might have been inherited with pathogenic mutations in PGRN effectively acting as a linked marker. Consistent with this hypothesis, sequence analysis of PGRN revealed that both the MAPT IVS10 + 29 and MAPT A239T cases also carried probable null mutations in PGRN (Fig. 2). The MAPT IVS10 + 29 case was found to have a PGRN Ex11 + 64C > T change that created a premature stop codon (Arg493X). This particular mutation is the most common mutation we have found to date with it being detected in nine separately ascertained cases (Gass et al., 2006). The MAPT A239T case contained a partial deletion of PGRN exon 11. The deletion starts 16 bp upstream from the exon and extends into the exon for 177 bp (IVS10-16, Ex11 + 177del194 bp). As the splice acceptor site is destroyed, we predict the effect of this deletion would be to splice out exon 11, resulting in an in-frame deletion of exon 11, thereby creating a shorter PGRN transcript and protein. Alternatively, it is possible that a frameshift occurs due to the presence of a cryptic splice acceptor site within the undeleted part of exon 11. However, in the absence of a source of mRNA, we were unable to determine the precise effect of this deletion.

The identification of probable null mutations in PGRN in combination with FTLD-U pathology with ub-ir NCI and NII indicates that the variants in MAPT reported in these cases (Pickering-Brown et al., 2002; Stanford et al., 2003), like that in PSEN1 (Amtul et al., 2002), are almost certainly rare benign polymorphisms, and are not responsible for disease. This has important consequences since this finding also questions the pathogenic significance of PSEN1 mutations that cause complete loss of function and
mutations in MAPT that increase the production of 3R tau. Collectively, the identification of PGRN mutations in cases previously thought to have mutations in MAPT and PSEN1 demonstrates that caution should be taken when interpreting the pathogenic significance of rare variants that cannot be confirmed by other methods especially when these are associated with an atypical clinical or pathological phenotype. A bias to detect rare variants can occur when disease genes are fully sequenced in disease cases, but only the frequency of specific variants is assessed in controls. The data presented here suggest full gene sequencing in controls is required to avoid this bias.

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References


