

## Clinical Heterogeneity Associated with Tau Gene Mutations

a report by

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It is now 10 years since the first descriptions of pathogenic mutations within the gene encoding the microtubule-associated protein tau (MAPT).<sup>1-3</sup> Over 60 different sequence variants have now been described, including splice-site and missense mutations and deletions, in both coding regions and introns, over 40 of which are thought to be pathogenic.<sup>4</sup> Prior to the identification of MAPT mutations, the umbrella term 'frontotemporal dementia with parkinsonism linked to chromosome 17' (FTDP-17) had been coined to describe autosomal-dominant kindreds linked to chromosome 17q21-22 with a highly penetrant disorder characterised clinically by a phenotype of frontotemporal dementia and parkinsonism.<sup>5</sup> The FTDP-17 nomenclature superseded the various clinical and clinicopathological labels previously applied to some of these kindreds, which included disinhibition-dementia-parkinsonism-amyotrophy complex, hereditary dysphasic disinhibition dementia, pallido-ponto-nigral degeneration, progressive subcortical gliosis and multiple system tauopathy with pre-senile dementia.

With the description of more MAPT mutations, the clinical and neuropathological heterogeneity of FTDP-17 cases has become increasingly apparent. An awareness of this clinical heterogeneity may be of importance to neurologists managing patients with neurodegenerative disease, informing differential diagnostic considerations and the need for tau gene mutation testing. A brief review of clinical variants associated with MAPT mutations may therefore be of pragmatic use; neuropathological features are not considered in this article, since these are generally available only *post mortem* and are hence of limited use in clinical practice.

### Clinical Phenotypes of MAPT Mutations

The 'classic' or 'prototypical' phenotype associated with MAPT mutations is a frontotemporal dementia syndrome with altered behaviour and personality, with additional parkinsonian features, hence 'FTDP'. Either the cognitive syndrome or the movement disorder may be more clinically evident. Prominent early epileptic seizures have been reported on occasion.<sup>6</sup>

The frequency with which tau mutations are identified in FTD patients varies depending on the source of the cohort examined, ranging from none in a community-based dementia series, to around 10% in cases of familial FTD, to 33% in familial FTD with confirmed tau pathology.<sup>7,8</sup> Phenotypes other than FTDP have also been described in association with MAPT mutations.

### Progressive Supranuclear Palsy

There have been a number of reports of patients with a phenotype of progressive supranuclear palsy (PSP) who are shown to harbour MAPT mutations, including R5L, N279K, ΔN296, G303V, S305S and IVS

10+16.<sup>9-15</sup> The PSP phenotype may be typical (i.e. conforming to widely accepted clinical research criteria for PSP) or atypical (e.g. absence of falls in the first year after symptom onset),<sup>14</sup> and cases may be familial or sporadic. In some cases, dementia has been late or questionable.<sup>15</sup> In one family, atypical PSP was associated with a homozygous mutation (ΔN296), and typical levodopa-responsive Parkinson's disease was observed in other family members with the heterozygous mutation.<sup>11</sup>

### Corticobasal Degeneration

The phenotype of corticobasal degeneration (CBD) has been described in association with the P301S and G389R MAPT mutations.<sup>16-18</sup> In the initial report, two family members carried the mutant P301S gene: a father with FTD and his son with CBD, both with age at onset in the late 20s.<sup>16</sup> In a Jewish-Algerian family with the same P301S mutation, cases with the typical FTDP-17 and CBD phenotypes were described; one patient with CBD was levodopa-responsive.<sup>17</sup> The G389R mutation, previously described in FTD cases, was found in a patient with sporadic corticobasal syndrome (no pathology available); his asymptomatic 87-year-old father also carried the same mutation, suggesting incomplete penetrance.<sup>18</sup>

### Idiopathic Parkinson's Disease

Cases diagnosed clinically as idiopathic Parkinson's disease (PD) but harbouring MAPT mutations have been reported on occasion (ΔN296, Q424K).<sup>4,11</sup>

### Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of a dementia syndrome. Although it is generally straightforward to distinguish AD from the canonical forms of FTD, differential diagnosis is not always easy since widely accepted clinical diagnostic criteria for AD and FTD show some overlap. Patients clinically diagnosed with AD who were subsequently found to have FTDP-17 with MAPT mutations have been reported, with the P301L, IVS10+16 and R406W mutations.<sup>19-24</sup> A patient with an AD phenotype who subsequently developed a PSP phenotype, leading to identification of the MAPT IVS10+16 mutation, has also been seen (Larner, unpublished observations). The ΔK280/ΔK281 sequence change has also been reported in a patient



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with AD, but the pathogenic significance of this MAPT sequence variant remains unclear.<sup>25</sup>

### Frontotemporal Dementia with Motor Neurone Disease

Two apparently unrelated families from the Basque country in Spain were reported with a phenotype of frontotemporal dementia with motor neurone disease (FTD/MND). Dysarthria was a common symptom at onset, and bulbar palsy with anarthria and dysphagia developed along with pyramidal signs and amyotrophy. Cognitive changes were late. Both families were found to harbour a MAPT mutation (K317M), and subsequent genealogical studies suggested a common ancestor.<sup>26</sup>

### Progressive Non-fluent Aphasia

Progressive non-fluent aphasia (PNFA) is the rarest of the cardinal syndromes of frontotemporal lobar degeneration. One pedigree bearing a MAPT mutation, V363I, has been described.<sup>27</sup>

### Respiratory Failure

In a highly inbred family from the travelling community in Yorkshire, England, two individuals presented with stridor, dyspnoea, aspiration pneumonia and respiratory failure. One patient apparently had additional mild parkinsonism and eye movement signs. *Post mortem* evidence of tauopathy prompted tau gene analysis, which showed the S352L mutation, the disorder apparently being inherited as a recessive trait.<sup>28</sup>

### Neurobiology and Pathophysiology

Dysfunction of tau, in terms of its binding to and assembly and stabilisation of microtubules, is thought to be the consequence of MAPT mutations, leading to neurodegeneration. However, the question remains as to the mechanism(s) by which mutations in a single gene, MAPT, produce the diverse clinical phenotypes outlined above. A similar question applies to the clinical heterogeneity seen in AD cases resulting from mutations in the presenilin 1 gene.<sup>29</sup>

It is well recognised that patients harbouring the same MAPT mutation may display different phenotypes, indicating that additional environmental and/or genetic factors may produce phenotypic variability on the background of an identical mutation. Examples include IVS10+16 manifesting with prototypical FTD,<sup>30,31</sup> or with an AD-like phenotype,<sup>22,24</sup>

or with PSP,<sup>14</sup> and the P301L mutation manifesting either with parkinsonian features or, more often, with behavioural changes such as disinhibition, aggression and personality change.<sup>32,33</sup> In two P301L patients with different phenotypes, differences in tau genotype were observed, which may possibly have been the factor modifying the phenotype.<sup>33</sup>

A study that examined the two common tau haplotypes, H1 and H2, found no evidence that they affected age at symptomatic onset or disease duration, but there was an association between the H1/H1 genotype and parkinsonian phenotype and between the H1/H2 genotype and the frontotemporal dementia phenotype, suggesting that tau genotype may predispose to specific clinical signs at disease onset.<sup>34</sup> Interestingly, the patient with the G389R mutation presenting with a sporadic CBD phenotype, rather than the FTD phenotype previously reported with this mutation, was H1-homozygous.<sup>18</sup>

Apolipoprotein E genotype does not appear to affect age at dementia onset in families with tau mutations,<sup>35</sup> unlike the situation in AD. However, possession of an apolipoprotein E  $\epsilon$ 4 allele has been associated with deposition of A $\beta$  deposits in the frontal cortex in FTD patients,<sup>36</sup> an observation that might be relevant to the AD-like phenotype seen with some MAPT mutations.

### Discussion and Conclusion

When should clinicians consider testing for MAPT mutations, other than in patients with a familial FTD syndrome, preferably with confirmation of tau pathology?<sup>7,8</sup> Although in general clinically and pathologically diagnosed cases of both familial and sporadic PSP do not have tau mutations,<sup>37</sup> the case may be made for MAPT testing in PSP patients with an atypical phenotype (e.g. very young onset, absence of falls in the first year after symptom onset) or a familial disorder. In other parkinsonian syndromes clinically resembling CBD or PD, the pick-up is likely to be extremely low and testing is not therefore recommended. Certainly, tau gene testing merits consideration in patients with a phenotype consistent with early-onset familial AD and who have proved negative for mutations in those genes (amyloid precursor protein, presenilin 1 and 2) known to be deterministic for early-onset familial AD.<sup>22,24</sup> In other frontotemporal lobar degeneration syndromes, such as the FTD/MND and PNFA phenotypes, the pick-up is likely to be very low. ■

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