Reviewer's report

Title: Role of the H1 haplotype of microtubule-associated protein tau (MAPT) gene in Greek patients with Parkinson’s disease

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Reviewer: John Kwok

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The authors describe the association study of the H1/H2 MAPT haplotypes in a case control cohort of 122 Greek Parkinson’s disease patients. They reported a significant association for the H1/H1 genotype (odds ratio = 1.566; p = 0.006), but not for two single nucleotide polymorphisms that tag H1 subhaplotypes (rs242562 and rs243207).

Major Compulsory Revisions

1) The use of appropriate H1 subhaplotype markers. The authors used rs242562 and rs243207 to tag H1 subhaplotypes as originally described in Skipper et al, 2004 paper. However, as the authors have discussed, the results for these two markers were contradictory for almost all subsequent reports, even after the analysis of the third Greek population as reported by this paper. I would suggest that a more productive way to select candidate polymorphisms would be to identify polymorphisms that have been shown to have a regulatory function in gene expression. For example fine mapping of the MAPT locus revealed that the polymorphism rs242557 within the H1c subhaplotype was the probable functional variant associated with Tau levels in cerebrospinal fluids [Laws SM et al. Fine mapping of the MAPT locus using quantitative trait analysis indentifies possible causal variants in Alzheimer’s disease. Mol Psychiatry 2007; 12: 510-517]. The use of this polymorphism may resolve some of the inherent contradictions of the multiple studies examining the effect of H1 subhaplotypes.

2) The use of statistical method as described in RESULTS section (paragraph 1, line 6) to look at the effect of sex on the association study. The method used by the authors is not a statistical adjustment, but rather, a stratification of the cohort by sex. This reduces the cohort size and statistical power for detecting association. Logistic regression analysis should be used to adjust for the effect of sex in their cohort.

Discretionary Revisions

1) There is no discussion of the apparent sex effect on the association between MAPT H1 haplotypes and disease risk, even it was observed by the authors and by the Fidani L. et al, 2006 study.

2) Clarification of the in DISCUSSION section (paragraph 2, line 13): “Since the association between the overall MAPT locus and PD has been well established, [18,27,31,35] it appears possible that MAPT interacts differently with other genes
of the MAPT region in different populations”. Could the authors clarify this statement? Do they mean that there are separate functional polymorphisms within the other genes within the extended the extended H1 haplotype? This issue is particularly relevant for the Q7R polymorphism in Saitohin gene is in linkage disequilibrium with the MAPT H2 haplotype and would be difficult to separate the effect of the Saitohin polymorphism and that of the MAPT H2 haplotype [Clark LN et al. The Saitohin ‘Q7R’ polymorphism and tau haplotype in multi-ethnic Alzheimer disease and Parkinson’s disease cohorts. Neurosci Lett 2003; 347: 17-20].

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests