Reviewer’s report

Title: Polymorphic genes of detoxification and mitochondrial enzymes and risk for progressive supranuclear palsy: a case control study

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Reviewer: Gunter Hoglinger

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Potts et al. propose the hypothesis that single nucleotide polymorphisms (SNPs) in genes encoding enzymes of xenobiotics detoxification, mitochondrial functioning or oxidative stress response are associated with PSP. They genotyped DNA from 553 autopsy-confirmed cases and 425 controls for SNPs in 10 candidate genes and found the proportion of NAT2 rapid acetylators compared to intermediate or slow acetylators larger in cases than in controls (OR 1.8; P < 0.05). The study indicates that alleles NAT2*5 and NAT2*6 might be protective and NAT2*4/*7 increase risk. The authors suggest that conversion of xenobiotics by NAT2 into toxic metabolites may be implicated in PSP.

Previous studies on potential risk of NAT2 genotypes in PSP have been controversial. While some found that slow metabolizers are associated with increased risk for neurodegenerative disorders, others found that rapid metabolizers convey increased risk, and yet other studies detected no effect. The proposed hypothesis is relevant and the careful analysis of high numbers of pathologically verified cases has to be emphasized.

Issues in the work of Potts et al.:
- No independent cohort was studied to confirm results
- The P value does not withstand correction for multiple testing.
- In the present manuscript, the authors argue that the SNP studied has not been on the chip used for the recently published GWAS. However, it is unlikely, that there was no single SNP to cover NAT2 on the chip. Most likely, the vast majority of cases studied here have already been included in the GWAS. Please verify the P-value and OR of the association of NAT2 in the GWAS data.

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:
please note that I have recently published with many of the authors of the present manuscript.