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: Matthias Elstner

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Background: Potts et al. herein present a genetic association study targeted at the detection of genetic risk factors in progressive supranuclear palsy (PSP). Published data suggests that xenobiotic and oxidative stress, as well as mitochondrial dysfunction may contribute to PSP. Therefore, the authors chose to analyze SNPs lying in a selection of genes that are encoding for enzymes of xenobiotic detoxification, mitochondrial dysfunction and oxidative stress response.

Methods: Data from 553 autopsy-confirmed Caucasian PSP cases were evaluated against 425 control samples. To our understanding, the authors determined frequency of 11 SNPs located in 7 genes: debrisoquine 4-hydroxylase (DYP2D6), paraoxonase (PON) 1&2, superoxide dismutase (SOD) 1&2, MAPT and the Parkinson genes DJ-1 and PINK. Although it is suggested in the abstract and the introduction that Parkin and DJ-1 were analyzed, no data is presented in the results section or mentioned in the discussion. Genotyping for these SNPs was done on the Sequenom Mass Array iPLEX platform. Additionally, N-acetyltransferase (NAT) 1&2 genotypes were determined using Taqman PCR methodology. NAT phenotypes were inferred from the genotype.

Main results: In this study, no significant association is reported for genotypes, except for rs1052553, a known association of MAPT HI in PSP. Also, NAT 1&2 genotypes were not different in cases and controls. Phenotypic analysis of NAT2 revealed an association with a higher proportion of rapid acetylators in PSP, when data for slow and intermediate phenotypes were combined (p=0.037). No adjustment for multiple testing was performed.

Reviewer’s general comments: The concept of this study is interesting in that the authors are trying to answer the important question of gene/environment risk factors in PSP. Despite the unquestionable advantage of GWAS studies there still is a necessity for such studies and certainly to report positive as well as negative findings. The case and control groups of this study are well characterized and group sizes should allow for the detection of an association of SNPs in candidate genes if there is one.

Minor essential revisions: Nevertheless, the selection of candidate genes seems a bit arbitrary and it could be helpful for the reader if this selection would be elucidated in more detail. Also, from the data presented, the abstract and
introduction seems misleading as to the analysis of Parkin and DJ-1.

Major Compulsory Revisions: In principle, this study showed no significant association of SNPs in the genes tested. However, negative results should generally be brought to public attention in an appropriate journal. Nevertheless, the main conclusion as brought forward by the authors (in the abstract and discussion), is that NAT2 rapid phenotype is associated with PSP. We do not believe this conclusion is justified on the basis of the presented data. As the authors state in their discussion, studies into the acetylator status in various disorders date back into the 90s with mixed results. NAT2 acetylator status was found to be (or excluded to be) associated with disorders ranging from colon cancer to Parkinson’s disease. Generally ‘fast acetylation’ seems favorable, although depending on the substrate some data indicate the opposite effect. Given the moderate p-value and the somewhat contra-intuitive finding, the explanation of the results presented seems circumstantial. Given this problematic background, the quantity of SNPs analyzed, as well as the statistical tests performed we believe correction for multiple testing would be essential. The explanation given as to why this was not necessary does not seem justified to us. Fundamentally, over 10 experiments (>10 SNPs plus NAT-analysis) were executed and this has to be corrected for. Otherwise, borderline significant p-values and spurious associations will appear by chance alone (p = 0.05 means 1/20 chance of false positive). In this specific case, correction would result in no significant association of the NAT-phenotype or a trend at best. Additionally, for justification of such a strong statement, findings would have to be verified in an independent cohort as generally considered a standard in genetic association studies. Such finding would truly advance the understanding of an underlying genetic susceptibility towards xenobiotic stressors in PSP.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.