Author's response to reviews

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

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Author's response to reviews: see over
Dear Editorial Team:

Thank you for your recent letter regarding our manuscript entitled “Polymorphic genes of detoxification and mitochondrial enzymes and risk for progressive supranuclear palsy: a case control study”. We appreciate the time and consideration that both you and the reviewers have given to our manuscript. We have noted the reviewers’ comments and revised the manuscript accordingly. Please note below our responses to each comment.

Reviewer #1 comments:

1. …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.

   The background section has been expanded to further explain the rationale behind our selection of candidate genes.

2. …the abstract and introduction seems misleading as to the analysis of Parkin and DJ-1.

   Text referring to these genes has been omitted as they were not included in the final iPLEX.

3. …we believe correction for multiple testing would be essential.

   Multiple testing corrections were performed using the Holm method for analyses modeled and analyzed together. With regard to the phenotype test it is important to note that these tests were modeled separately from the SNPs and considered to be independent tests. Furthermore, only two phenotypes were compared, therefore no multiple testing corrections were needed. This is consistent with how NAT2 phenotype analysis has been previously reported by Hein and colleagues [see references 46, 57, 58].

Reviewer #2 comments:

1. No independent cohort was studied to confirm results.

   In the conclusions we have included the following statement to point out the need for confirmation with an independent cohort:

   “…as 514 of the PSP cases analyzed here were also included in the GWAS, this finding should be confirmed in an independent cohort.”

2. The p-value does not withstand correction for multiple testing.
3. …Please verify the P-value and OR of the association of NAT2 in the GWAS data.

Statistics were not provided for NAT2 in the GWAS due to lack of significance. We have also provided rationale differentiating our study from the GWAS:

“Furthermore, our results are consistent with the recent genome-wide association study (GWAS) on PSP that did not find any associations with SNPs rs1043424, rs662, rs7493 or any individual NAT2 SNPs…when we used the SNPs to input NAT2 phenotype we observed a significant association between imputed rapid NAT2 acetylator phenotype and PSP. This result is important since this method of testing NAT2 phenotype association with disease has been shown to be more useful than looking at individual SNPs [57, 58]. Thus, our study is quite different from the GWAS, and with respect to NAT2, much more powerful in terms of biological plausibility.”

Associate Editor’s comments:

1. Correction for multiple testing should be applied even when this leads to a negative result

Please see the response to this concern above under Reviewer #1. This data has been analyzed by a statistician

2. Provide details on how many of your cases were included in the recent GWAS, and why your locus was not indicated at least by nearby chips

We clarified in the manuscript that the PSP samples studied here were also included in the GWAS:

“…as 514 of the PSP cases analyzed here were also included in the GWAS, this finding should be confirmed in an independent cohort.”

We have indicated the specific NAT SNPs analyzed and identified the markers that were also included in the GWAS. It is important to note that unlike the GWAS, we used the NAT SNPs to form phenotypes.

3. Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.

We addressed this concern by adding the following statements:

“All samples were from adults over age 33 (see Table 1 for demographic information). Institutional review board (IRB)-approved protocols, including informed consent, were followed to obtain all DNA samples.”
We thank you and the reviewers for the thoughtful comments. We believe that our revised manuscript has significantly improved and hope you now find it ready for publication in *BMC Medical Genetics*. We look forward to hearing from you.

All the very best,

Irene Litvan, M.D.

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