Author’s response to reviews

Title: Role of t-PA and PAI-1 Variants in Temporal Lobe Epilepsy in Chinese Han Population

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Author’s response to reviews:

Dear Prof. Benjamin Ragen,

Thanks for your letter and reviewers’ comments concerning our manuscript entitled “Role of t-PA and PAI-1 variants in temporal lobe epilepsy in Chinese Han population” (Manuscript No.: NURL-D-18-00101). The comments are very valuable and all the suggestions have been carefully considered. All changes made to the text are marked in red color. We hope this revised version will have sufficient quality for acceptance by BMC Neurology. The main corrections and the point-by-point response to the reviewer’s comments are as follows:

1. Peer-Reviewer #1:

1) This is potentially interesting study but the authors should also perform check for possible population stratification (in spite of ethnically matched controls) and, more importantly, perform
correction for multiple comparisons (Bonferroni adjustment). This should increase the validity of their findings.

RE: Firstly, thanks for your consideration and reminding us of performing check for possible population stratification and Bonferroni adjustment for multiple comparisons. We totally agree with your suggestion, but the data obtained after population stratification may not be representative due to our relative small sample size. Therefore, we performed Bonferroni adjustment for multiple comparisons to ensure the validity of our findings, and the changes that we have made are highlighted in red words in the results and discussion session of our manuscript (See page 6 and 7 in details).

2) It would be also preferable if they included the second (independent) group of patients to show they were able to replicate this finding. (I understand that this may not be feasible for the authors) but they should at least comment on this.

RE: We are agreed with your suggestion on including the second group of patients to ensure the replication of our finding. As its infeasibility for us in the limited time, we have commented on this and highlighted in red word in discussion session (See page 11 in details).

2. Peer-Reviewer #2:

1) These findings will provide a useful contribution to the literature, but the current presentation could be improved to facilitate the reader's understanding of the findings, as outlined below. Briefly, further information in the introduction section and interpretation in the discussion section and clarification of the tables would help the manuscript.

RE: Thanks for your comments on our manuscript and we have revised the introduction section, the discussion section and the tables accordingly. The details have been marked out in red word in the manuscript (See page 3, 4, 8 and the Revised Table in the attachment in details).

3. Additional requests/suggestions:

1) In the introduction section, the authors should provide some statement as to what t-PA and PAI-1 are, what they do under normal circumstances, and how alterations in expression could promote the occurrence of seizures. Such information will strengthen the rationale of the study.

RE: To strengthen the rationale of our study, we have specified what t-PA and PAI-1 are, what they do under normal circumstances, and how alterations in expression could promote the occurrence of seizures (See page 3 and 4 in details).
2) In the introduction, the authors describe increased expression of t-PA and PAI-1 following seizures in animal models and in human postmortem tissue. Therefore, one would predict that the t-PA polymorphisms described in this study would lead to increased expression of t-PA and/or increased t-PA release, as the authors briefly mention in the discussion section. Please discuss the nature of the polymorphisms and how they might lead to increased occurrence of TLE in further detail in the discussion.

RE: We have discussed the nature of the polymorphisms and their influences on the level of its encoded protein, and the various mechanisms leading to increased occurrence of TLE due to the alteration of protein level in further detail in the discussion (See page 8 in details).

3) In the last paragraph of the discussion, the authors wrote, "Unfortunately, we failed to find a significant difference in genotypic and allelic frequencies of polymorphic site PAI-1 in rs1799768 between TLE and control groups." I suggest you delete the word "unfortunately", as use of this word suggests a bias approach to the study.

RE: The word “Unfortunately” in the last paragraph of the discussion has been deleted considering your suggestion (See page 10 in details).

4) In the current form, Tables 2 and 3 are quite difficult to interpret. I suggest splitting each table into one table for genotype and one table for allele. Also, I suggest a footnote under each allele table or an indication at the top of each allele table indicating the number of subjects and the number of alleles (i.e., "Cases (242 alleles across 121 subjects (% of population)"). In the current form, it is confusing to the reader why the total number of samples for the bottom three rows of each of Tables 2 and 3 totals greater than the number of samples listed at the top of the column.

RE: To increase the readability of tables, we have split each table into one table for genotype and one table for allele and added an indication at the top of each allele table indicating the number of subjects and the number of alleles according to your suggestion (See the Revised Table in the attachment in details).

5) This manuscript would benefit by editing.

RE: To improve the quality of the article, the manuscript has been edited (See all the text in the manuscript in details).
With Best Regards,

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