Author’s response to reviews

Title: Associations of genetic variation in CASP3 gene with noise-induced hearing loss in a Chinese population: a case-control study

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Author’s response to reviews:

Dear David Ozonoff,

Thanks for the copy-editing of our manuscript entitled "Associations of genetic variation in CASP3 gene with noise-induced hearing loss in a Chinese population: a case-control study" (ENHE-D-16-00364). We truly appreciate the in-depth criticisms and constructive comments from the reviewer. Based on the reviewer’s comments, the revised manuscript has been carefully proofread. The attached please find a detailed reply to reviewers’ comments. And changes to the original manuscript are marked with 'tracked changes'. If you need any more information concerning the manuscript please do not hesitate to contact us.

We are looking forward to hearing from you.
Following are our replies to the queries.

Reviewer #1:

1. Please submit the results of the stratified analysis by noise intensity and CNE as well as SNP-SNP interactions.

   Answer: According to the advice by the reviewer, we submit those results in the additional file 1 as Table S1, S2 and S3, and have revised the sentences accordingly. Please see line 9–10, paragraph 3, line 12–13, paragraph 4 of the results section.

2. Many studies have confirmed that there is a interaction between noise and gene which contribute to the development of NIHL. This study only found the significant interaction between working time and SNP. CNE is related to working time. Please explain the reason.

   Answer: According to the results of our study, we did not observe significant interaction between CNE and SNP. This may due to one limitation of our study as we have mentioned in the discussion part. Due to limited conditions, we used factory, fixed-point measurement of noise level for individual noise exposure values, which may have affected the accuracy of the results. This could possibly explain why we didn’t found interaction between CNE and SNP.

3. In the table 3, for rs1049216, the combined CT/TT genotypes were protective genotypes. While in the table 4, authors found that CC genotype was risk genotype combined working >48 hours/week. Authors were suggested to have a consistent conclusion. There is the same problem for rs6948.
As shown in table 3, there were three genotypes for rs1049216, CC, CT and TT. When compared with CC genotype, the combined CT/TT genotypes were protective genotypes. Thus if the reference genotype were the combined CT/TT genotypes, the CC genotype was the risk genotype. Besides, working ≤ 48 hours/week was usually considered as a protective factor when compared with working >48 hours/week for NIHL. Thus we take the low risk combination which were CT/TT genotypes combined with working ≤ 48 hours/week as the reference group in the crossover analysis. And the results showed that CC genotype combined working >48 hours/week was risk factor of NIHL, which was consistent with the results of table 3. So did rs6948.

4、If the author conduct 1:1 matched case-control study, I suppose the case and control subjects should be matched by the basic characteristics (gender, age, and et al) and environmental factors (years of noise exposure, types of work, music listening time, telephone using time and time go to sleep) to ensure highly comparability in basic and environmental confounders. Therefore, the differences in the hearing loss found in this study between case and control subjects mainly caused by genetic susceptibility. But significant differences were observed for several lifestyle factors including music listening time, telephone use time, and time to go to sleep between the cases and controls (P<0.05) in this study.

Answer: Usually in case-control study, we did use the matching technique to make the two groups as comparable as possible. However, we were not able to balance all possible confounding factors between the two groups. Firstly, the difficulty of conducing the study will increase and the research efficiency will decrease as the number of controlled factors increase. Usually this is called overmatching. Secondly, the possible effect of those controlled factors cannot be evaluated. Since we can evaluated and adjusted their effect by statistical method such as logistic regression, the controls in our study were matched with gender, age, and years of noise exposure one for each case. And logistical regression was used to compute the adjusted OR with 95% CI to evaluate the association between the SNPs and NIHL risk in our study.

5、I suppose the case subjects should be defined as the average of binaural HL in high frequency is over 40dB. Authors were suggested to consider expanding the sample size.

Answer: As we have explained in the last letter, we adopted this definition of cases based on previous studies (e.g. 1. Prevalence of hearing loss and differences by demographic characteristics among US adults: data from the National Health and Nutrition Examination