Author's response to reviews

Title: Genetic Variation of NEDD4L Is Associated with Essential Hypertension in Female Kazakh General Population: A Case-Control Study

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**Point-by-point responses**

Q1: The characteristics of the participants should be described precisely. Especially, the amount of salt should be described or discussed in the comparison with other races, such as Han Chinese. This is a critical point to consider the function of NEDD4L in the pathogenesis of hypertension.

A: Thank you very much. There is a previously published study (China National Nutrition and Health Survey in 2002) that compares other populations (including Mongolian, Hui, Tibetan, Uygur, Miao, Yi, Zhuang, Buyi, Man, Yao, and Tujia) with the Kazakh population, showing the latter has a higher dairy salt intake (average daily consumption > 21g). The China National Nutrition and Health Survey in 2002 was a well-designed, large sample study and the findings are reliable. Therefore, we did not repeat the investigation of salt intake in Kazakh and cannot quantify the amount of salt in this study.

Q2: The mean age of the participants in this study is quite young to discuss the predisposition to hypertension in general population. Thus, the morbidity of hypertension and the mortality of cardiovascular disease in Kazakh population should be shown in forties to seventies.

A: As is known, the pathogenesis and genetic background of essential hypertension is different from secondary hypertension. It is an important cue to suspect secondary hypertension if the onset age of hypertension is < 30 years or > 60 years. Therefore, participants < 30 or > 60 years of age were excluded from this study.

Q3: The excess salt intake associates with not only hypertension but also obesity and diabetes. In the basic characteristics of cases, the frequency of obese, dyslipidemia and hyperglycemia were significantly higher than that in controls, suggesting that NEDD4L increased risk for volume retention or visceral obesity. These possibilities are also examined in the data analysis and discussion.

A: Thank you again. The associations between the SNPs and overweight, dyslipidemia, hyperglycemia, and central obesity were also examined respectively, and no significant associations were found in this study (Supplement Table 3).
Q1: The authors provide a mechanism that possibly explains the gender-specific findings, but it would also be appropriate to include in the discussion whether any previously published reports have found gender-specific effects of gene variants in general (and the gene variants reported in this manuscript in particular) on blood pressure traits, particularly significant gene-by-gender interactions. It would lend support to their findings.

A: Thank you very much. There are several previously published studies that have reported gender-specific effects of gene variants and gene-by-gender interactions on human hypertension. I have revised it according to your suggestion.

Q2: I did not see data for a statistical test of the gene-by-gender interaction in the results section. It would seem that to conclude there is a difference between men and women with respect to the effect of the genetic variants on hypertension one would need to test for an interaction.

A: Thank you again. I have performed gene-by-gender interaction on blood pressure traits according to your suggestion. A significant interaction between NEDD4L genotype and gender ($P$ for interaction: 0.045 for rs2288775 and 0.064 for 296921-296923delTTG) was found in this study. I have rephrased it according to your suggestion.

Q3: There is a striking difference between men and women for self-reported smoking status in this study population - over 50% of men and only about 1% of women report being smokers according to Table 2. It would be interesting to know whether the apparent gene-by-gender interaction is only a proxy for an underlying gene-by-smoking interaction – there is some prior work on gene-by-smoking interactions; for example the NHLBI Family Heart Study has reported on a genotype-by-smoking interaction on calcified coronary atherosclerosis. The authors could try stratifying the data by smoking status rather than gender to see if differences are observed. They could also perform a statistical test of the gene-by-smoking interaction and compare it to a statistical test of the gene-by-gender interaction to see which is stronger.
A: We have assessed the interaction effects of gender and SNPs on blood pressure traits, as well as interactions of smoking and SNPs according to your suggestion. There was a significant interaction between NEDD4L genotype and gender (P for interaction: 0.045 for rs2288775 and 0.064 for 296921-296923delTTG), but no significant interaction between NEDD4L genotype and smoking was found (P for interaction: 0.616 for rs2288775 and 0.447 for 296921-296923delTTG). These suggest that the gender-specific and gene-by-gender interaction findings in this study are reliable. I have revised it according to your suggestion.

Q4: Table 3 would be improved if column percentages were added to the allele frequency data.
A: Thank you very much. I have rephrased it according to your suggestion.

Q5: Quality of written English: Not suitable for publication unless extensively edited
A: This manuscript has been edited by international Science Editing (http://www.internationalscienceediting.com/).