Author's response to reviews

Title: Serum uric acid distribution according to SLC22A12 W258X genotype in a cross-sectional study for a Japanese general population

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Author's response to reviews: see over
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Editor of BMC Medical Genetics

Dear Editor

Thank you very much for the useful comments on the manuscript entitled “Serum uric acid distribution according to SLC22A12 W258X genotype in a cross-sectional study for a Japanese general population”.

The manuscript was revised according to the comments. The response to each comment is described in separate sheets.

I would greatly appreciate it if you consider the revised manuscript as a research article of BMC Medical Genetics.

Sincerely

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Thank you for the comments. The responses are as follows.

**Editorial requests:**

Authors’ contributions were revised according to the instruction as below.

“NH conceived of the study, participated in the design and coordination, and drafted the manuscript. MN and KW participated in the design and coordination, edited the data, and drafted the manuscript. RO contributed the genotyping, establishing PCR primers and PCR conditions for *SLC22A12* W258X. AH and YA participated in the coordination, organizing the informed consent process and data/sample collection. All authors read and approved the final manuscript.”

**Referee 1:**

The comment is correct in terms of a biological sense, but this study provided new findings epidemiologically.

Referee 2:

I thank the reviewer for the useful comments to improve the manuscript. The responses to the comments are as below.

**Major Compulsory Revisions**

1. The authors indicated that distribution of SUA between individuals with WW and WX was different (Table 2). However, the distribution of factors that exert effect on SUA (BMI, age, triglyceride, blood sugar, etc.) may be different between groups. The authors should show that the frequencies of these factors in individuals with WW or WX as much as possible.

Table 2 was added to show the difference in age, BMI, blood pressure, and blood tests. The below sentences was inserted as the second paragraph of Results.

“The means of age, BMI, blood pressure, and blood tests according to the genotype and sex are listed in Table 2. The null hypothesis that the means were equal among the
three genotypes was rejected with one-way ANOVA for creatinine and glucose in males, and for age and gamma-glutamyltransferase (GGT) in females. When the WX and XX were combined, the difference in the mean between the combined and the WW became nonsignificant for GGT in females, but still significant for creatinine and glucose in males and age in females.

In addition, the adjustment of creatinine and glucose in males and GGT in females was conducted. The results were added in the last of Results as below.

“When these ORs were adjusted for creatinine and glucose in males and for GGT for female, no substantial differences were observed; for example, the OR of SUA < 3 mg/dL for X allele was 89.8 instead of 102.5 in males and 30.7 instead of 25.6 in females.”

2. The authors stated that “The effect of X allele on SUA was significantly larger in males than in females” in the first paragraph of Discussion. However, is it correct?

It is well known that females show lower SUA because of the uricosuric action of estrogen. I think that the SUA-lowering-effect of X allele in males is similar to that in females, but the effect looks stronger in males because of the lower levels of estrogen in males.

I understand this comment based on a biological sense. Since the description “The effect of the X allele on SUA was significantly larger in males than in females.” was simply based on the observation “The difference in mean SUA between WX and WW genotypes was 2.27 mg/dL in males and 1.19 mg/dL in females.”, the sentences were corrected as below.

In the second paragraph of Results, “(F=45.25, d.f.=1, 5017, p=2E-11)” was inserted after “The difference in mean SUA between WX and WW genotypes was 2.27 mg/dL in males and 1.19 mg/dL in female”.

In the first paragraph of Discussion, “The difference in mean SUA between WX and WW genotypes was 2.27 mg/dL in males and 1.19 mg/dL in females, indicating that the reduction of the mean SUA due to possessing a X allele was significantly larger in males than in females.”
3. The authors described that SLC22A12 258X seemed to be a major contributor of SUA levels in Japanese. The authors clearly showed that the distribution of SUA in individuals with WW was different from that in individuals with WX. However, the proportion of individuals with X allele is too small. The data provided here is not sufficient to show that 258X is a “major” contributor of SUA in Japanese.

I agree the comment. The sentence in the third sentence, “Accordingly, SLC22A12 258X seemed to be a major contributor influencing SUA among Japanese.” was revised to “Accordingly, SLC22A12 258X seemed to be one of the important genetic traits influencing SUA among Japanese.”

Minor Essential Revisions
1. Background line 6: The authors have to check the sentence “… and physical conditions the factors associated…”

Thank you for the comment. The sentence “Accordingly, lifestyle and physical conditions the factors associated with SUA levels” is unnecessary. It was deleted from the manuscript.

Discretionary Revisions
1. It is interesting that the SUA distribution of WW females is similar to that of WX males. It may suggest that the effect of X allele on SUA is comparable to the effect of estrogen. It is better to discuss that point in Discussion section.

I greatly appreciate this comment. The below sentence was inserted in the first paragraph of Discussion.

“Since the distribution among the females with WW genotype was closer to that among the males with WX genotype (Table 3), the effect of X allele on SUA may be compatible in size to the sex difference.”

Expressions were revised as below
1. In Abstract: “Those with WX genotype was 14 (77.8%) of 18 males with a SUA of 1.0–2.9 mg/dL, and 28 (34.6%) of 81 females with the same range of
SUA.”

2. In Subjects and data collection: “The health checkup data including blood tests were used for this study. Peripheral blood was drawn in the morning from those _fasting_ overnight.”

3. In Genotyping: “The amplified DNA fragments were 117-base pairs (bp) for the \( W \) allele (\( G \) allele), 176-bp for the \( X \) allele (\( A \) allele), and 255-bp for a common band, as demonstrated in Figure 1.”

4. In Statistical analysis: “Means among three genotype groups were tested with _analysis of variance (ANOVA)_.”

5. In Results: “Those with a SUA less than 3.0 mg/dL were 0.6% in males and 5.2% in females, while those with a SUA of 7.0 mg/dL or over were 23.5% in males and 1.5% in females. The genotype frequency was 4,793 for \( WW \), 225 for \( WX \), and 5 for \( XX \), which was in Hardy-Weinberg equilibrium (\( p=0.164 \)); the \( X \) allele _frequency_ was 0.023 (95% CI, 0.021-0.027 ).”

6. In Discussion: “This study demonstrated the SUA distribution according to the \( SLC22A12 \) \( W258X \) genotype in a Japanese general population.”

7. In Discussion: “The difference in the mean SUA between \( WX \) and \( WW \) genotypes was 2.27 mg/dL in males and 1.19 mg/dL in females,”

8. In Table 1: a number was corrected (91 to 90), which was found through the re-analysis for this revision.