Author’s response to reviews

Title: Contiguous 22.1-kb deletion embracing AVPR2 and ARHGAP4 genes at novel breakpoints leads to nephrogenic diabetes insipidus in a Chinese pedigree

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Author’s response to reviews:

Editor Comments:

The reviewers and the editor believe that this is an interesting study. However, the quality of manuscript should be improved by 1) checking grammar and all statistics carefully, unifying the reference format, and 3) discussing the limitation of the study. Response: We greatly appreciate the positive comments of the editor and reviewers on our manuscript. According the comments of the editor and reviewer, we have improved our English writing and statistical analysis; unified reference style and discussed limitations of the study. Please find corresponding responses as following.

BMC Nephrology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Kunling Ma (Reviewer 1): Reviewer, Kunling Ma: This study aimed to investigate mutations in arginine vasopressin type 2 receptor (AVPR2) which causes congenital X-linked nephrogenic diabetes insipidus (NDI). Results demonstrated that A novel 22,110 bp deletion comprising AVPR2 and ARH4GAP4 genes was identified by PCR mapping, long range PCR and sanger sequencing. The deletion happened perhaps due to the 4-bp homologous sequence (TTTT) at the junctions of both 5’ and 3’ breakpoints. The gross deletion co-segregates with NDI. The authors concluded that identified a novel 22.1-kb deletion can lead to X-linked NDI in a Chinese pedigree, which would increase the current knowledge in AVPR2 mutation.

This study is an interesting clinical study which mainly reported a novel 22.1-kb deletion in AVPR2 mutation led to X-linked NDI in a Chinese pedigree.
Q1: The authors should expand the scope of investigation for this Chinese pedigree to get more evidence.

Response: We greatly appreciate the comments of the reviewer. According to the reviewer’s advice, we have added more clinical data of the proband based on his medical record. However, due to the limitation of previous under-developed medical care in China, the clinical data of other two NDI patients were unavailable. Moreover, adult patients refuse further lab examination for NDI. The data that we added are as following:

“The 24 h urine volume was 9 L, and specific gravity of urine was 1.003. Urine osmolality was 75 mOsmol/L and failed to rise after 24 h water deprivation (91 mOsmol/L).” (Page 4, Line 7-9)

“Howevers, treatment failed at the age of 13 year and his parents refused further treatment.” (Page 4, Line 11-12)

“Serum concentration of glucose, electrolytes (Na+, K+, Ca2+, Cl-), urea nitrogen and creatinine, complete cell blood count as well as plasma osmolality were all in the reference range. Moreover, neither electrocardiogram nor brain magnetic resonance imaging showed anomaly.” (Page 4, Line 16-19)

Q2: Statistical analysis should be done in this study.

Response: We have added statistical analysis to the method and result sections as well as figure legends in our revised manuscript.

“Relative DNA level was expressed by mean. DNA level between patients was compared by Cruskal-Wallis H test. All statistical analyses were performed using IBM SPSS Statistics 22.0 software, and P < 0.05 was considered statistically significant.”(Page 5, Paragraph 3)

“Compared with unrelated female control, the proband’s mother showed a 50%-reduction in the copy number of AVPR2 gene, while the proband showed no amplification of AVPR2 (P = 0.027, Figure 3).” (Page 6, Last line)

“Compared with unrelated female control, in III:5 DNA level of AVPR2 gene was decreased by half, while no PCR product was generated in IV:4 (P = 0.027).” (Page 13, Last line)

Q3: Limitation for this study should be discussed in the section of Discussion.

Response: We have discussed the limitation for this study in our revised manuscript (Page 8, Paragraph 2):

“There are several limitations in our study. First, due to unavailability of previous clinical records, the developmental data of other patients from the NDI pedigree could not described in this study. Second, the impact of the gross deletion on cell functions of renal tubular epithelial cell was not examined. Therefore, further experimental studies on the biological significance of AVPR2 or ARHGAP4 deletion are needed.”
Q4: Some grammar errors should be corrected.
Response: We have corrected all grammar and spelling errors as possible as we can.

Q5: The format of references should be unified.
Response: We have unified the format of references in our revised manuscript.

Chun Zhang (Reviewer 2): The authors found a novel gross deletion spanning AVPR2 and ARHGAP4 genes in a Chinese pedigree with X-linked nephrogenic diabetes insipidus, and discussed the potential function of this deletion in short stature. The experiment was well designed and the overall manuscript is easy to follow. This is an interesting report. There are, however, some points, which need to be addressed by the authors.

1. There are some grammatical mistakes in the manuscript.

Line 27 on page 2: "After available data analysis" should be "After analyzing available data".

Line 51 on page 3: "we review all characterized entire AVPR2 deletions and find the potential." is suggested to be modified as "we reviewed all characterized AVPR2 deletions and found the potential."

Line 19 and line 27 on page 4: The past perfect tense should be changed to past tense in "urine osmolality had also been measured" and "nosebleeds had happened...".

Line 1 on page 6: "combination" in "After PCRs using different primer combination" should be "combinations".

Line 7 on page 6: "using by UCSC Genome Browser..." is suggested to be modified as "according to Human Feb. 2009 <GRCh37/hg19> Assembly on UCSC Genome Browser".

Line 29 on page 6: "Compared to" should be "Compared with".

Line 53 on page 6: It is obscure in this sentence: "Especially the proband was small for his age verified by X-ray."

Line 56 on page 6: "comparing" should be "compared".

Line 16 on page 7: "need further investigated" should be "need to be further investigated".

Multiple demonstrative pronouns such as "it" and "these" are not used properly.

Response: We have corrected all grammar and spelling errors as possible as we can.
2. The reference format is not concordant with the style of BMC Nephrology. Please refer to the instructions here: https://bmcnephrol.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article.

Response: Reference style has been formatted in our revised manuscript according to the requirement of BMC Nephrology.