Author's response to reviews

Title: The variations of VP1 protein might be associated with nervous system symptoms caused by enterovirus 71 infection

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Author's response to reviews: see over
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Dr. Philippa Harris
Editor
BioMed Central

Dear Dr. Harris

Thanks again for your time for reviewing and considering our manuscript for publication in BMC Infectious Diseases. We have addressed the reviewers’ queries in our revised manuscript point-by-point accordingly. For your convenience, we have shown the changes in red.

I wish we have fully addressed the queries and satisfied the reviewers.

Sincerely Yours,

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Reviewer 1
Major compulsory revisions

1. Fig 2. The methods to draw the 3D structure should be written in Methods and figure legend.

Response: Thanks very much for your constructive suggestions. We have added a paragraph to describe the methods for drawing 3D VP1 structure in the Methods section (page 4, line 16 - 20).
We also revised the legend of Fig 2 (page 13, line 21 - 26).

2. Discussion, pg7, line 18-19. EV-71 could potentially spread through neural route to the brain. It also infects other cells, not just neurons.

Response: We have revised the sentence (page 7, line 23; and page 8, line 1-3)

3. Discussion to include limitations such as only about 180 isolates were chosen and that genotypes distribution have geographical restrictions.
Response: As suggested, we have added a paragraph to discuss the limitation in this study and possible solution in the future (page 9, last paragraph).

4. References format. Inconsistent formatting.
Response: The references format was adapted according to BMC Infect Dis.

Minor essential revisions
1. Pg 4, line 7. Change to the date of Sep 30, 2012 to “as of”
Response: The sentence was revised as proposed.

2. Table 1. Can be placed as Supplementary table.
Response: Table 1 was placed in the supplementary, as Supplementary Table 2.

3. Discussion, pg 4, line 15. Change “neuron” to neural.
4. Fig 2 figure legend. Starts with capital.
Response: The point 3 and 4 were revised as reviewer proposed.

Reviewer 2
Major Compulsory Revisions
1. Page 6, table 3, did the authors consider Bonferroni correction for multiple comparisons in Chi-square? After Bonferroni correction, only T292N/K remains statistically significant. Page 8, line 10, "At this site, N292 is the consensus sequence for subgenotype of B1 and B2, which did not present in other genotypes." This seems to be in line with the Bonferroni correction result, which only T292N is statistically significant. Can the authors address this?
Response: Yes. Only T292N/K remains statistically significant after Bonferroni correction, as reviewer pointed out. We don’t adopt the methods because (1) the cases is not too large. (2) the comparisons (N value ) is small.

2. Page 6, are there any other consensus substitutions for subtype B1, B2, and B3, since these subtypes were correlated with nervous system complications in the previous result?
Response: There is no other consensus substitution for subtype B1-3.

3. Page 7, line 13, "It has been reported that D164E variation was associated with severe cases of EV71 infection....." This previous finding is not consistent with the current finding in this study, which shows E164D/K was associated with nervous...
system infection. Can the authors address this?

Response: In the previous paper, the variation comparison is not based on the genotype, and the cases is small (only 56). Furthermore, severe cases contained kinds of symptoms, such as death, shock, and nervous system infection. In this study, we narrowed down to neural infection, and analysis is based on the genotype of EV71.

Minor Essential Revisions

1, Page 4, line 7, "Sep 30, 2012" or 2013?

Response: We collected up to Sep 30, 2012 instead of 2013. Because this study took us near 1 year.

2, Page 5, line 8, "B4-5 in Malaysia". According to supplementary Fig 1A, B5 in Taiwan or Japan?

Response: Subtype of B4-5 mainly took place in Malaysia although there are sporadic reports in Taiwan and Japan. We have revised the sentence.

3, Page 5, line 11, "subgenotype" or "subtype"? Can the authors make it consistent throughout the text, including figure legends and tables?

Response: In the text, all “subgenotype” was changed into “subtype”