

Dear Dr. Ying Dou:

Thank you for your decision letter on our submitted manuscript (ID:51170) entitled “Multisystem Smooth Muscle Dysfunction Syndrome in China: A Case Report and Review of Literature”. We would like to thank the reviewers for their constructive and positive comments and suggestions for revision of the manuscript.

We have revised the manuscript accordingly and it is attached to this letter for your consideration. All amendments are highlighted in red text in the revised manuscript. In addition, point-by-point responses to the reviewers' individual comments are listed below.

We hope that the revision is now acceptable for the publication in your journal and look forward to hearing from you soon.

Yours sincerely,

Corresponding author:

Yuqing Wang

E-mail: wang\_yu\_qing@126.com.

## **Responses to Reviewer's comments**

1. In description of the case report, it is advisable to write the case presentation in paragraph form for continuity of the manuscript.

Response: Thank you for this comment. The case presentation of this article was written in the order of chief complaints, past history, personal history, family history, physical examination, laboratory examinations and imaging examinations in paragraph form as the journal required.

2. Clinical images can be added.

Response: Thank you for this comment. The patient's clinical images of chest HRCT, Cranial MRI, abdominal ultrasonography, echocardiography, bronchoscopy and gene sequence analysis have already been added in this manuscript in page 7 to 9.

3. Discussion can be altered to focus on the differences/novelty of this case presentation compared with the previous documented cases.

Response: Thank you for this comment. In the cardiovascular system, our patient had only patent foramen ovale in the early stage and had pulmonary artery dilatation during follow-up without PDA or pulmonary hypertension, which was different from other cases. Our patient had skin and mucosal symptoms, which manifested as cyan-purple plaques on her right face, buccal mucosa, oral tongue and palate which was not reported before. These differences have been already mentioned in the discussion.

4. Discuss the long term consequences of the condition and the

management if any, for the same.

Response: Thank you for this comment. Five deaths had been reported in all cases. Our patient's management and present situation were added in page 19.

5. Sequencing of the patient's and parent's DNAs shows the mutation is heterozygous in ACTA2 c.536G>A (p.R179H) and an independent de novo event in the patient in Fig. 6. ACTA2 is located on the minus strand of chromosome 10. Thus the DNA sequence shown in the figure is complementary to the gene: 536C>T. This information should be provided in the figure legend.

Response: Thank you for this comment. The complementary DNA sequence was added in this article in page 9.

6. The patient has two copies of the gene with 536G (normal: 179R) and 536A (mutation: 179H). It is very important to check if the mutated copy of the gene is expressed. If so, how much is the mutant copy expressed compared to the normal wild type?

Response: Thank you for this comment. Transcriptome sequencing had not been done because of technology limitations. Therefore, we can't figure out how much the mutant copy was expressed.

7. The previous findings of the disease are summarized well in Table 1. This table should, however also include the current case findings of this study and discuss how similar or different they are from the previous

findings.

Response: Thank you for this comment. I have added the symptoms of each system in this case to Table 1 as required. Our patient had dyspnea, recurrent upper respiratory tract infection, congenital fixed dilated pupils, pulmonary artery dilatation, development delay and gallstone which were also reported in the previous cases. Our patient had patent foramen ovale and pulmonary artery dilatation without PDA and pulmonary hypertension, which was different from other cases. Our patient had skin and mucosal symptoms, which manifested as cyan-purple plaques on her right face, buccal mucosa, oral tongue and palate. The similarities and differences above have been mentioned in the discussion.