Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: This report by He et al. describes a case of chronic pseudoileus in a 43 year old male patient of Chinese origin. Whole exome sequencing (WES) revealed the presence of MYH11 mutation, a rare condition linked to primary visceral myopathy and chronic intestinal pseudo-obstruction (CIPO). The topic is highly relevant to the scope of the journal and may be of significant interest for the readers. However, there are several issues that need to be addressed before this article may be considered fit for publication:

1. Overall, the manuscript is poorly written and there are many grammatical and language errors. In particular, several sentences are too long and may be split into two or even three separate sentences. At the same time, few sentences appear to be incomplete as they end abruptly (e.g The first sentence of the Background section). In fact, many parts of the manuscript need to be completely re-written/re-framed to make it easier for the readers to comprehend the scientific content. Help may be sought from a native English speak or a language editing service.

Response: Thank you for pointing this out. In order to make it easier for readers to understand the scientific content, we have rewritten almost the entire manuscript, especially those sentences that were too long and incomplete.

2. Several changes need to be incorporated in the manuscript based on the "CARE" checklist. As of now, it is evident that the guidelines have not been followed. (For example, "case report" is not added to Keywords, there is no Table or Figure of timeline, no 'take-away' message, Limitations or Conclusion, etc.)

Response: Thanks for your suggestion. We have added "case report" to keywords, added 'take-away' and 'Conclusion' to the manuscript. The take away message from this case is that the doctors can take clinical routine examination, CT test, combined with WES test for early diagnosis of CIPO patients, so that treatment can be carried out in the early stage of the disease. The conclusion: In this case, mechanical ileus and secondary causes of pseudoileus were excluded, and the location, nature and extent of the lesions were examined by small bowel CT examination. Whole exome sequencing determined the etiology and found a rare mutation MYH11 (NM_001040113.1: c.5819delC (p.Pro1940Hisfs*91). This case provides clinicians with an understanding and genetic basis for the etiology of CIPO.

3. The last part of the 'Abstract' section can be improved and re-framed.

Response: Thanks for your suggestion. We have improved the Abstract.

Abstract: A 43-year-old male Han-Chinese patient with recurrent abdominal distention without significant cause for 15 years. The physical and biochemical parameters examinations, as well as the other relevant examination results showed no obvious abnormalities. Contrast-enhanced computed tomographic (CT) showed a huge duodenum,

obvious expansion of intestinal lumen, and chronic intestinal pseudo-obstruction. Whole exome sequencing (WES) analysis of the patient and her mother confirmed the diagnosis of primary familial visceral myopathy type 2 chronic pseudoileus with a rare heterozygous gene mutation in MYH11. This is the second CIPO case with a MYH11 (NM_001040113.1: c.5819delC (p.Pro1940Hisfs*91) heterozygous mutation. The take away message from this case is that the doctors can take clinical routine examination, CT test, combined with WES test for early diagnosis of CIPO patients, so that treatment can be carried out in the early stage of the disease.

4. The last four lines of the 'Background' section may be removed and replaced by some general information about the MYH11 gene mutation and WES. Source of this information must also be provided in the references.

Response: Thanks for your suggestion. We have removed the last four lines of the 'Background' section, and add some general information about the *MYH11* gene mutation and WES. Source of these information also have been provided in the references.

5. The results of physiological and biochemical tests of the patient may be summarized in the form of a Table rather than describing in the text. Some word appears to be missing in the following line "24H urine 19.49 mmol/24h". SI units should be used throughout.

Response: Thank you for pointing this out. We have summarized the results of physiological and biochemical tests of the patient in Table 1 and 2.

6. Methodology of WES is entirely missing. If it was performed commercially, it should be clearly mentioned. What about the data analysis? Relevant details must be provided.

Response: Thanks for your suggestion. The WES was performed commercially to the BGI company in Shenzhen, China. We have written the relevant information in the manuscript. We performed WES to detect presence of any mutation(s) in the related disease-causing genes. 2ml of blood in ethylenediamine tetraacetic acid (EDTA) coated tube was sent to the ShenZhen BGI Medical Test Laboratory.

7. Figure legends and the corresponding descriptions need to be written clearly. PDB identifiers for the structures must be provided.

Response: Thanks for your suggestion. We have written the message in the legends of Figure 2. The three-dimensional structure of the wild-type MYH11 protein and the MYH11 protein sequence with p.Pro1940Hisfs*91 mutation by SWISS-MODEL, a fully automated protein structure homology-modelling server. The mutant protein is extended by 91 amino acids, resulting in the change circled in red circle.

8. In Figure 2 depicting the 3D protein model, some changes can also be seen in other parts of the protein (beyond the red circle). Are they due to the difference in angle of viewing? If not, what is the explanation?

Response: Thanks for your question. We use the fully automatic protein structure homology modeling server, SWISS-MODEL to analyze the 3D structure of the protein.

Since the 3D model is automatically generated, we cannot adjust the angle. Therefore, some changes can also be seen in other parts of the protein. In fact, the end of the mutant protein is extended by 91 amino acids, resulting in the change circled in red.

9. The information about the MYH11 mutation which has been provided in the "Case Report" section may be moved to the 'Background' section.

Response: Thanks for your suggestion. We have move the information *MYH11* mutation from "Case Report" section to the 'Background' section.

10. Some information mentioned in the 'Discussion' section may be moved to the 'Background' section. The rate of incidence may be reported as "one in _____" rather than in decimals.

Response: Thanks for your suggestion. We have rewritten the dissection section of this manuscript. The rate of incidence also has been changed. Due to considerable phenotypic heterogeneity, the estimated incidence of CIPO is 1/476190 and 1/416666 in men and women respectively.

Reference：

Iida H, Ohkubo H, Inamori M, Nakajima A, Sato H: **Epidemiology and clinical experience of chronic intestinal pseudo-obstruction in Japan: a nationwide epidemiologic survey**. *J Epidemiol* 2013, **23**(4):288-294.

11. It will be worthwhile to describe previous studies where MYH11 mutation has been reported in CIPO cases. Are the results similar? If there are any differences, they should be compared and discussed along with the message for other gastroenterologists and physicians should they encounter a similar case.

Response: Thanks for your suggestion. We have described and compared previous studies where MYH11 mutation has been reported in CIPO cases in DISSCTION section of this manuscript. In addition to the pseudo-intestinal obstruction, this patient also had symptoms of urinary retention, which may be related to the abnormal smooth muscle cell function caused by the *MYH11* gene mutation. In clinical work, visceral myopathic pseudointestinal obstruction caused by *MYH11* gene mutation is rare. In a previous study, the mutations in MHY11 were frameshift，the first was a 2 bp deletion in exon 22 (c.2809_2810del, p.Arg937Glyfs*7, paternal), while the second mutation in exon 26 was a 49 bp deletion (c.3422_3470del, p.Lys1141Thrfs*20, maternal). Katja et al. reported a MMIHS patient with a novel heterozygous missense variant c.379C>T in *MYH11*. In another case, the MHY11 mutation was is a frameshift mutation in exon 42 (NM_001040113.1: c.5819delC, p.Pro1940HisfsTer91). In this case, WES was used to analyze the patient and found a rare autosomal dominant mutation in MYH11, NM_001040113.1: c.5819delC (p.Pro1940Hisfs*91), which was consistent with the result of a previous case. This study strengthens our understanding of the CIPO etiology and provides genetic evidence for doctors to diagnose CIPO.

12. The case report ends abruptly. A brief conclusion may be added at the end.

Response: Thanks for your suggestion. We have added a 'conclusion' section to the end of

the manuscript. Conclusion: In this case, mechanical ileus and secondary causes of pseudoileus were excluded, and the location, nature and extent of the lesions were examined by small bowel CT examination. Whole exome sequencing determined the etiology and found a rare mutation MYH11 (NM_001040113.1: c.5819delC (p.Pro1940Hisfs*91). This case provides clinicians with an understanding and genetic basis for the etiology of CIPO.

Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The authors described a case of MYH11 frameshift related chronic intestinal pseudo-obstruction syndrome. The description is clear. Some revision will make it better.

Major issue: 1. Please recheck the data. The frameshift is detected by Sanger sequencing in Figure 3. However, the true mutation site in not correctly indicated by the red arrow.
Response：Thanks for your suggestion. We have rechecked the data and found the site is correct. The CDS length of MYH11 is 5838 bp, and the heterozygous mutation, a frameshift mutation caused by the deletion of one nucleotide C at position 5819 of the gene coding sequence. The red arrow points the nucleotide C at position 5819 of the gene coding sequence.

Minor issue: 1. It will be better to give more description about the method of how you perform and analyze the WES data. Which pipeline is used for mapping, variant calling and interpretation.
Response: Thanks for your suggestion. The WES was performed commercially to the BGI company in Shenzhen, China. We have written the relevant information in the manuscript. We performed WES to detect presence of any mutation(s) in the related disease-causing genes. 2ml of blood in ethylenediamine tetraacetic acid (EDTA) coated tube was sent to the ShenZhen BGI Medical Test Laboratory. The sequencing was performed using capture high-throughput chip technology, detection of almost 20000 genes in the human genome. Sanger sequence were used to verify the mutations.