

Peer Review File

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Reviewer #1

This is a concise report for recently identified variants of EPCAM gene in CTE patients. Good descriptions of each patient history will be helpful for pediatricians to be aware this rare disease. The authors also reviewed previous cases and summarized the distribution and mutation type of pathogenic EPCAM mutations in Chinese population. The reviewer has minor concerns that can be revised as listed below.

Comment 1: English grammar needs to be reviewed and fixed by a native speaker. For example, in line 25: All patients “presented (no with)” congenital diarrhea and “needed” PN because of growth retardation even when diarrhea “was” improved.

Reply 1: Thank you very much for your review and valuable suggestions. We have corrected the grammar errors throughout the manuscript based on your advice.

Changes in the text: Throughout the article.

Comment 2: By WES, were other CODE genes than CTE confirmed not having pathogenic variants? Please discuss.

Reply 2: Yes, there were no other CODE genes than CTE confirmed to not have pathogenic variants. We have added explanations to the discussion section.

Changes in the text: Page 9, lines 208-209

Comment 3: Scale bars and identification of biopsy tissues (colon vs. duodenum) must be added to Figure 2 and 3.

Reply 3: Thank you for this suggestion. Scale bars and identification of biopsy tissues have been added to Figure 2 and Figure 3.

Changes in the text: Figure 2 and Figure 3.

Comment 4: Microvillus inclusion disease is now broadly called MVID, not MID.

Reply 4: The abbreviations have been modified.

Changes in the text: Page 8, lines 197

Page 9, line 200-201

Comment 5: “EPCAM” protein must be non-italic. Please review entire manuscript carefully and distinguish EPCAM protein vs. EPCAM gene.

Reply 5: The abbreviations have been modified.

Changes in the text: Throughout the manuscript.

Comment 6: Line 75: Introduction uses MOC31 instead of EPCAM, which is used later text. Please add an explanation that MOC31 is same gene product as EPCAM.

Reply 6: MOC31 is a monoclonal antibody of EPCAM. We have added an explanation to the introduction section.

Changes in the text: Page 4, line 67

Comment 7: Line 110: How old the patient 1 when the laboratory test was done?

Reply 7: The laboratory tests in Table 1 were done when patients were admitted to our hospital. Patient 1 was at the age of seventeen months when his mother brought him to our hospital.

Changes in the text: There were no modifications made to the original text. Please see Page 4, line 75 and Page 5, line 82

Reviewer #2

Comment 1: This seems most consistent with a case series rather than an “original article” as described.

Reply 1: Thank you very much for your review and valuable suggestions. We have cancelled one patient from our reporting, according to the author instruction, our article reporting of three patients might be classified as a “case report”. And we have restructured the article to the instructions. Because we contain a detailed review of 11 patients and statistical analysis, we wonder if our article could be published as an “original article”. We will accept your decision.

Comment 2: There are numerous grammatical errors that need to be corrected.

Reply 2: Thank you for your careful review. We apologize for the grammar errors, which have been corrected in the revised version.

Comment 3: The inclusion of 3 vs 4 patients is inconsistent.

Reply 3: Initially, there were four cases, but one of them (Patient 2 in the first manuscript, Patient 1's elder brother) had not been treated in our hospital. We only had his gene testing (WES) report and then inquired with his mother for information about his disease history and recent condition. His diarrhea symptom had been alleviated, and he was off PN eventually. We thought this case had a certain clinical value and included him in this analysis. But due to his incomplete data, we finally decided to exclude this case (Patient 2 in the first manuscript). So, we finally included three patients in this study.

Changes in the text: Relevant parts (in red) of introduction and discussion sections.

Comment 4: The "coagulant function abnormalities" need to be expanded upon to describe whether this was due to Vitamin K deficiency or true hepatic synthetic dysfunction.

Reply 4: The coagulant function abnormalities were due to hepatic synthetic dysfunction, which could not be corrected by transfusions of vitamin K but by transfusions of frozen plasma.

Changes in the text: Page 8, lines 188-190

Comment 5: The degree of PN support and how long patients remained on PN (and to what degree) needs to be better described.

Reply 5: We have added the details about current PN for Patient 2 and Patient 3 in terms of the degree and the duration.

Changes in the text: Page 6, lines 121-123

Page 7, lines 141-143

Comment 6: This seems most consistent with a case series rather than an "original article" as described. I think the decision to publish hinges on whether the editor is looking for a case series or not.

Reply 7: Please see our responses to comment 1.

Comment 7: CTE is rare, and it is interesting to hear a single institution's experience with several cases, but it is not clear what makes this case series stand out beyond what has been published in the literature before. Perhaps what is more unique to this article is detailing the natural history of CTE if PN (or at least full PN) is not provided, but this could be emphasized more. If the editor is interested in adding to the cases reported in the literature, this would be appropriate for publication with revisions.

Reply 7: There were cases published in the literature before, but most of them were only with one case. We have summarized 3 patients and reported five novel mutations. Besides, as you

have noted, it was more unique that the natural history of CTE was detailed, in terms of the degree and duration of PN. According to your suggestion, we emphasized these points.

Changes in the text: Page 6, lines 121-123

Page 7, lines 141-143

Page 8, lines 172

Page 9, lines 228-230

Table 2

Comment 8: The article should be reviewed for language editing as there are multiple typos that likely arise from English being the authors' second language.

Reply 8: Thank you for your advice. We had the article reviewed for language editing again.

Comment 9: The distinction between the 3 and 4 patients is inconsistent in the text. Since ultimately 4 patients are included, the number of patients should be consistently used as 4 when appropriate (ex, Line 80).

Reply 9: We apologize for the unclarity. The final number of patients included in this article is three. Please refer to our response to comment 3.

Changes in the text: Relevant parts (in red) of introduction and discussion sections.

Comment 10: Line 89-91: I do not think this sentence from line 89-91 is necessary and it only serves to add confusion to the story.

Reply 10: Yes, we excluded the Patient 2 in the last manuscript and deleted the part of him and that sentence.

Comment 11: Line 114: The way that the upper endoscopy is introduced is odd. I would say: "An upper endoscopy with biopsies was performed and revealed gross villous atrophy in the duodenum."

Reply 11: Thank you. We have modified this sentence as you suggested.

Changes in the text: Page 5, lines 85-86

Comment 12: Line 117: Focal clusters of what?

Reply 12: We meant focal clusters of epithelial cells. We have modified this expression in the article.

Changes in the text: Page 5, line 87-88

Comment 13: Line 124: Expand on the specific indications for starting PN. Dehydration, malnutrition, both?

Reply 13: Indications for starting PN included both of dehydration and malnutrition. We have modified this sentence accordingly.

Changes in the text: Page 5, line 93

Comment 14: Line 125: Expand on the reason for sepsis. Was it a central line associated bloodstream infection?

Reply 14: Sepsis was associated with bloodstream infection and controlled with antibiotics.

Changes in the text: Page 5, line 94-95

Comment 15: Line 126-127 are confusing. Why was the patient taken off PN at discharge? Does this institution not support home PN?

Reply 15: We agree that it was misleading in the context and we have modified our text. Yes, we could not offer home PN supporting service in our center, and this is also our direction of efforts. The mother was worried about complications of PN, such as infection, and believed that this child could get better with her attentive care as his elder brother did, who had the same mutations. Thus, despite our persuasion, she decided to take the child home, fed him with rice gruel, and gradually added other foods. The child still has mild diarrhea but is growing very slowly. Patient 2 and Patient 3 in this revision manuscript, had partial PN at home. That was because the mother of the Patient 2 was a nurse and created a condition of partial PN at home, and Patient 3 was hospitalized and received PN for 2 months and went back to the U.S. to obtain the service of home PN.

Changes in the text: Page 5, lines 96-97

Comment 16: Line 128: Why is pork specifically mentioned?

Reply 16: Because it is the first meat that could be tolerated.

Comment 17: During the summary of Patient 1, it might be worth mentioning his developmental milestones. Does he have any developmental delays?

Reply 17: His mother said the intelligence development of the boy was normal for children of the same age, but she could not remember the definite time when her baby could walk or call "Mom" and "Dad."

Changes in the text: Page 5, lines 102

Comment 18: Line 145: Please mention Z-scores for this patient's measurements.

Reply 18: As this patient was excluded for incomplete data, this part has been deleted. Z-scores for 3 patients in the revision manuscript were demonstrated.

Comment 19: Line 145-146: "he had no diarrhea until the time of this study"—what does this mean?

Reply 19: We meant that he had no diarrhea currently. As this patient was excluded for incomplete data, this part has been deleted.

Comment 20: Line 148-149: I would mention his age in weeks instead of months and days.

Reply 20: The statement as you suggested is more intuitive and we have modified as you suggested.

Changes in the text: Page 5, line 104

Comment 21: Line 149-150: The sentence beginning "The frequency of watery stools..." should be re-worded.

Reply 21: We have revised this sentence.

Changes in the text: Page 5, line 105-106

Comment 22: Line 150-154: The discussion of treatments should be moved to after his symptoms and growth parameters.

Reply 22: In lines 150-154, those treatments were given to him before he was transferred to our center. The growth parameters were after those treatments and at the time when he was admitted to our center. We elaborate this in the article as "When admitted to our center."

Changes in the text: Please see Page 6, line 109

Comment 23: All discussion of "coagulant function abnormalities" need to be expanded upon. Is this an elevated prothrombin time and INR? Was it Vitamin K responsive? It needs to be made clear if this was from a Vitamin K deficiency or hepatic synthetic dysfunction.

Reply 23: The coagulant function abnormalities were from hepatic synthetic dysfunction. We have clarified this in the article.

Changes in the text: Page 8, lines 188-190

Comment 24: Line 161: Gastrointestinal endoscopy: I would specify that this patient had an EGD and colonoscopy performed.

Reply 24: We have modified this sentence.

Changes in the text: Page 6, line 114-115

Comment 25: Line 170-171: I would state the PN composition as ml/kg and kcal/kg for better reference. Also please state the reason for partial PN. Was this because he did not require full PN or was this due to social factors? Again, it is unclear if this institution supports home PN or whether this patient was coming into the center to get infusions.

Reply 25: The patient could take some food and had partial PN. The PN composition has been stated as ml/kg and kcal/kg, as you suggested.

Changes in the text: Page 6, lines 121-123

Page 7, lines 141-143

Comment 26: Line 172: It does not seem necessary to list the specific foods in his diet.

Reply 26: We removed this part and replaced with “digestive diets.”

Changes in the text: Page 6, lines 120-121

Comment 27: Line 175: Is this while on partial PN? If so, this should be specified.

Reply 27: Yes, he is still on partial PN currently, and this has been specified in the article.

Changes in the text: Page 7, lines 141-143

Comment 28: Line 186: Were these laboratory tests on admission? This should be specified.

Reply 28: These laboratory tests were on admission.

Changes in the text: Page 6, line 130

Comment 29: Line 187: “The other findings were normal” is vague.

Reply 29: We mean that the results of other tests were normal. We have modified this sentence.

Changes in the text: Page 6, line 131

Comment 30: Line 189: Specify that these are gross/visual findings on endoscopy rather than histologically.

Reply 30: These are gross/visual findings on endoscopy.

Changes in the text: Page 6, line 132

Comment 31: Line 200-201: Please provide Z-scores for growth parameters.

Reply 31: We thought that the current growth of this child was basically at a normal level, so we did not report specific Z-scores. We have included them in the revised manuscript.

Changes in the text: Page 7, lines 141-143

Comment 32: Line 305-307: How can mutations in exon 3 be more common across all populations if mutations in exon 5 were ranked first?

Reply 32: We apologize for the unclarity. Researchers revealed that the exon regions in which the most frequent pathogenic variants varied for different parts of the world. Variants in the Middle East are often in exon 5, whereas in East Asia, exon 3 pathogenic variants are more frequent. For the patients in China, exon 3 pathogenic variants are indeed the most frequent.

Changes in the text: Page 9, line 216-218

Comment 33: Figure 4: Consider removing the numbers on the pie chart sections themselves, as it is confusing.

Reply 33: We have removed the numbers on the pie chart as advised.

Changes in the text: Figure 4

Comment 34: Table 1: Since Patient 2 is being included in the analysis, I would include their demographics and laboratory information in this table.

Reply 34: Patient 2 in the last manuscript has not been hospitalized in our hospital and was excluded for incomplete data in this revision.