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## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 105347

**Title:** Protein-losing enteropathy and multiple vasculature dysplasia in LZT Y-related Noonan syndrome: A case report and literature review

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 08117080

**Position:** Peer Reviewer

**Academic degree and professional title:** Assistant Professor, Associate Research Scientist, Lecturer, Research Assistant Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** China

**Manuscript submission date:** 2025-01-24

**Reviewer chosen by:** Hong-Xin Jiang

**Reviewer accepted review:** 2025-02-26 14:20

**Reviewer performed review:** 2025-03-04 07:29

**Review time:** 5 Days and 17 Hours

<b>Content to be reviewed</b>	Does the manuscript's content fall within the scope of the journal? <b>Yes</b> Is there any Key Word that is not included in the manuscript title? <b>No</b> Do authors' affiliations correspond to the content of the manuscript? <b>Yes</b> Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b>
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Are the Key Words complete? **Yes**

Is the content of the Introduction adequate? **Yes**

Is the content of the Materials and Methods complete?  
**Yes**

Is the description of the experiments clear and  
complete? **No**

Are the experimental data presented in the  
manuscript's biostatistics content reliable? **Yes**

Are the experimental data of the Results true and  
reliable? **Yes**

Are the quality and resolution of the images up to  
standard? **Yes**

Do the selection and design of the figures and tables  
follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the  
manuscript and between the main text and the content  
presented in the figures and tables? **Yes**

Are the figures and tables numbered consecutively in  
the order in which they appear in the manuscript? **Yes**

Is the content of the Discussion reasonable? **No**

Is the Conclusion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **No**

Are all references related to the topic of the  
manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers?  
**Yes**

Are additional experiments needed for the study? **No**



	Does the research scope comply with ethics? <b>Yes</b>
<b>Scientific quality</b>	Grade A (Excellent)
<b>Novelty of this manuscript</b>	Grade C (Good)
<b>Creativity or innovation of this manuscript</b>	Grade B (Very Good)
<b>Scientific significance of the conclusion in this manuscript</b>	Grade B (Very Good)
<b>Language quality</b>	Grade B (Very good)
<b>Does this manuscript describe a study of the existing knowledge system?</b>	Yes
<b>Does this manuscript report a revolutionary innovation?</b>	No
<b>Does this manuscript report an unconventional innovation?</b>	Yes
<b>Conclusion</b>	Major revision
<b>Re-review</b>	Yes
<b>Peer-reviewer statements</b>	Peer-Review: Anonymous
	Conflicts-of-Interest: No

**SPECIFIC COMMENTS TO AUTHORS**

Reviewer comments Firstly, this manuscript reports a case of a patient who was hospitalized multiple times due to recurrent edema and diarrhea caused by hypoproteinemia. Subsequently, a rare mutation in the LZTR1 gene was identified through a series of clinical and laboratory examinations. Finally, based on the clinical information and whole-exome sequencing, the patient was diagnosed with Noonan syndrome and received appropriate treatment, thereby further expanding the phenotypic spectrum of hypoproteinemia associated with Noonan syndrome. This study



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is a valuable case report closely following current research trends which variants in the LZTR1 gene are associated with Noonan syndrome. While, there are a number of problems with the novelty and structure of the paper, along with some issues with format and choice of words. Question 1 The most significant highlight of the paper lies in the discovery of an LZTR1 gene mutation associated with Noonan syndrome. However, this variant has already been reported in reference 19, which substantially diminishes the novelty of the article. The authors should place greater emphasis on the differences from previously reported cases and explore the potential molecular mechanisms by which LZTR1 gene mutations may lead to hypoalbuminemia in result and discussion? Question 2 It is recommended that the author carefully revise the grammatical structure of the article and incorporate appropriate conjunctions in suitable places to further enhance the readability of the text and pique the interest of the readers. Abstract The abstract is poorly written and lacks clarity in its logic. Given that the abstract is the most significant part of an article, it is recommended that the authors reorganize the case report according to the patient's diagnostic and treatment process, and add appropriate connecting words or transitional phrases where necessary. 1. Abstract, CASE SUMMARY, line 2: " Whole-exome sequencing revealed a heterozygous mutation (c.850C>T, p.Arg284Cys) in LZTR1, suggesting Noonan syndrome type 10". You should specify which exon of the LZTR1 gene the variant is located in? 2. Abstract, CASE SUMMARY, line 5. When a technical term first appears in a manuscript, it should be written out in full followed by its abbreviation in parentheses, for example "CT", as well as the subsequent 3-D and PET-CT, etc. 3. Abstract, CASE SUMMARY, line 9. It is recommended that the author phrase it as follows "Further examination revealed that the patient suffers from protein-losing enteropathy, intestinal lymphangiectasia, and dysplasia of the thoracic duct". 4. Abstract, CASE SUMMARY, Last sentence. It is advisable to add the conjunction "moreover" or other word before the



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last sentence, as this will enhance the fluency of the text. INTRODUCTION

1.Introduction, para 2, line 2: The authors need to add the OMIM number for Noonan syndrome after mentioning the disease. CASE PRESENTATION 1.CASE

PRESENTATION, Laboratory examinations: It is recommended that the authors provide a pedigree of the family. The author may assess the impact of this mutation on the

LZTR1 protein by querying databases such as MutationTaster, PolyPhen-2, and VarCards. Furthermore, the author should present the whole exome sequencing data

and include the figure obtained from sanger sequencing. The author may endeavor to

utilize certain bioinformatic prediction tools (for example CLUSTALW (<https://www.genome.jp/tools-bin/clustalw>) and AlphaFold2) to forecast the influence

of this variant on the structure of the LZTR1 protein. Ultimately, the author should ascertain the pathogenicity of the variant (“Benign”, “Likely Benign”, “Uncertain

Significance”, “Likely Pathogenic”, “Pathogenic”) according to the ACMG 2015 guideline. DISCUSSION 1. Discussion, para 2: It is suggested that the authors provide a

more detailed discussion on how the LZTR1 gene variant affects the RAS-MAPK and ERK signaling pathways, thereby leading to the corresponding clinical symptoms in the

patient. In addition, the authors should discuss more about the differences between this case and those previously reported. 2.Discussion, para 3, line 11: What does this sentence

“however, only a higher educational qualification was received” mean? 3. Discussion, para 4: Do the authors have any relevant literature or data to support their speculation

that vascular malformations and brachydactyly are new symptoms of Noonan syndrome?



**PEER-REVIEW REPORT**

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 105347

**Title:** Protein-losing enteropathy and multiple vasculature dysplasia in LZT Y-related Noonan syndrome: A case report and literature review

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer’s code:** 05755618

**Position:** Peer Reviewer

**Academic degree and professional title:** FACP, MD

**Reviewer’s Country/Territory:** Japan

**Author’s Country/Territory:** China

**Manuscript submission date:** 2025-01-24

**Reviewer chosen by:** Hong-Xin Jiang

**Reviewer accepted review:** 2025-03-07 03:34

**Reviewer performed review:** 2025-03-08 12:18

**Review time:** 1 Day and 8 Hours

<b>Content to be reviewed</b>	<p>Does the manuscript’s content fall within the scope of the journal? <b>Yes</b></p> <p>Is there any Key Word that is not included in the manuscript title? <b>No</b></p> <p>Do authors’ affiliations correspond to the content of the manuscript? <b>Yes</b></p> <p>Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b></p> <p>Are the Key Words complete? <b>Yes</b></p>
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Is the content of the Introduction adequate? **No**

Is the content of the Materials and Methods complete?  
**Yes**

Is the description of the experiments clear and complete? **No**

Are the experimental data of the Results true and reliable? **Yes**

Are the quality and resolution of the images up to standard? **Yes**

Are the experimental data presented in the manuscript's biostatistics content reliable? **Yes**

Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **No**

Is the content of the Discussion reasonable? **Yes**

Is the Conclusion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **No**

Are all references related to the topic of the manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers?  
**Yes**

Are additional experiments needed for the study? **No**

Does the research scope comply with ethics? **Yes**

Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **Yes**



Scientific quality	Grade B (Very good)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade B (Very Good)
Scientific significance of the conclusion in this manuscript	Grade B (Very Good)
Language quality	Grade B (Very good)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	Yes
Does this manuscript report an unconventional innovation?	Yes
Conclusion	Major revision
Re-review	Yes
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

### SPECIFIC COMMENTS TO AUTHORS

A 15-year-old female was hospitalized multiple times due to recurrent edema and diarrhea secondary to hypoalbuminemia. Ultimately, whole-exome sequencing revealed a heterozygous mutation in LZTR1 (c.850C>T, p.Arg284Cys), leading to a diagnosis of Noonan syndrome type 10. Further investigations into the recurrent edema and diarrhea associated with hypoalbuminemia identified protein-losing enteropathy, intestinal lymphangiectasia, and thoracic duct hypoplasia. The authors performed microsurgery for thoracic duct outlet obstruction caused by thoracic duct malformation. Following surgery, over approximately two years of follow-up, her edema and diarrhea improved,



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and she maintained normal liver biochemistry. This case report is an intriguing account of Noonan syndrome with a rare genetic abnormality, accompanied by a literature review. However, several concerns are raised: Introduction: The introduction should include an explanation of Noonan syndrome for readers unfamiliar with the condition, in addition to describing protein-losing enteropathy. For example: Noonan syndrome occurs in 1 in 1,000–2,500 live births. It is a hereditary disorder caused by abnormalities in genes involved in the Ras/MAPK signaling pathway. Features include distinctive facial characteristics, congenital heart defects, short stature, and intellectual disability. There is no definitive treatment; management focuses on symptomatic therapy. Prognosis depends largely on the severity of associated heart disease. Differential Diagnosis: Was celiac disease or Crohn's disease excluded as potential causes of protein-losing enteropathy? Were upper and lower endoscopies, capsule endoscopy of the small intestine, or fluoroscopic evaluations performed? Including relevant images would enhance clarity. Literature Review: Summarize cases of Noonan syndrome with protein-losing enteropathy in a table and discuss them in the text. It is likely that a few such cases exist. Patient Privacy: Ensure that identifiable features in facial photographs are obscured except for the eyes' position to protect patient privacy. Family Pedigree: Provide a family pedigree diagram and tables detailing specific genetic sequences. Mutation Distribution: Illustrate the distribution of genetic mutations with diagrams marking mutations (e.g., with asterisks). Surgical Technique: Include detailed descriptions of the microsurgical procedure for thoracic duct outlet obstruction and provide illustrative diagrams of the surgical approach.



**RE-REVIEW REPORT OF REVISED MANUSCRIPT**

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 105347

**Title:** Protein-losing enteropathy and multiple vasculature dysplasia in LZT -related Noonan syndrome: A case report and literature review

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer’s code:** 08117080

**Position:** Peer Reviewer

**Academic degree and professional title:** Assistant Professor, Associate Research Scientist, Lecturer, Research Assistant Professor

**Reviewer’s Country/Territory:** China

**Author’s Country/Territory:** China

**Manuscript submission date:** 2025-01-24

**Reviewer chosen by:** Yu-Fei Wei

**Reviewer accepted review:** 2025-04-03 08:23

**Reviewer performed review:** 2025-04-03 13:34

**Review time:** 5 Hours

<b>Content to be reviewed</b>	<p>Does the manuscript’s content fall within the scope of the journal? <b>Yes</b></p> <p>Is there any Key Word that is not included in the manuscript title? <b>No</b></p> <p>Do authors’ affiliations correspond to the content of the manuscript? <b>Yes</b></p> <p>Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b></p>
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Are the Key Words complete? **Yes**

Is the content of the Introduction adequate? **Yes**

Is the content of the Materials and Methods complete?  
**Yes**

Is the description of the experiments clear and  
complete? **Yes**

Are the experimental data presented in the  
manuscript's biostatistics content reliable? **Yes**

Are the experimental data of the Results true and  
reliable? **Yes**

Are the quality and resolution of the images up to  
standard? **Yes**

Do the selection and design of the figures and tables  
follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the  
manuscript and between the main text and the content  
presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in  
the order in which they appear in the manuscript? **Yes**

Is the content of the Discussion reasonable? **Yes**

Is the Conclusion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **No**

Are all references related to the topic of the  
manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers?  
**Yes**

Are additional experiments needed for the study? **No**



	Does the research scope comply with ethics? <b>Yes</b>
<b>Scientific quality</b>	Grade A (Excellent)
<b>Novelty of this manuscript</b>	Grade A (Excellent)
<b>Creativity or innovation of this manuscript</b>	Grade B (Very Good)
<b>Scientific significance of the conclusion in this manuscript</b>	Grade A (Excellent)
<b>Language quality</b>	Grade A (Excellent)
<b>Does this manuscript describe a study of the existing knowledge system?</b>	Yes
<b>Does this manuscript report a revolutionary innovation?</b>	No
<b>Does this manuscript report an unconventional innovation?</b>	Yes
<b>Conclusion</b>	Accept
<b>Peer-reviewer statements</b>	Peer-Review: Anonymous
	Conflicts-of-Interest: No

### SPECIFIC COMMENTS TO AUTHORS

After carefully reviewing the manuscript's scientific quality, language quality, and adherence to ethics standards, the author has revised the manuscript in accordance with the suggestions from the editor and reviewers. The manuscript has met the requirements for acceptance.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 105347

**Title:** Protein-losing enteropathy and multiple vasculature dysplasia in LZT -related Noonan syndrome: A case report and literature review

**Provenance and peer review:** Unsolicited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05755618

**Position:** Peer Reviewer

**Academic degree and professional title:** FACP, MD

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** China

**Manuscript submission date:** 2025-01-24

**Reviewer chosen by:** Yu-Fei Wei

**Reviewer accepted review:** 2025-04-03 15:48

**Reviewer performed review:** 2025-04-04 13:38

**Review time:** 21 Hours

<b>Content to be reviewed</b>	Does the manuscript's content fall within the scope of the journal? <b>Yes</b> Is there any Key Word that is not included in the manuscript title? <b>Yes</b> Do authors' affiliations correspond to the content of the manuscript? <b>Yes</b> Does the Abstract contain the contents of each part of the manuscript (IMRaD)? <b>Yes</b> Are the Key Words complete? <b>Yes</b>
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Is the content of the Introduction adequate? **Yes**

Is the content of the Materials and Methods complete?  
**Yes**

Is the description of the experiments clear and complete? **Yes**

Are the experimental data presented in the manuscript's biostatistics content reliable? **Yes**

Are the experimental data of the Results true and reliable? **Yes**

Are the quality and resolution of the images up to standard? **Yes**

Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Yes**

Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **Yes**

Is the content of the Discussion reasonable? **Yes**

Is the Conclusion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **No**

Are all references related to the topic of the manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers?  
**Yes**

Are additional experiments needed for the study? **Yes**

Does the research scope comply with ethics? **Yes**



Scientific quality	Grade A (Excellent)
Novelty of this manuscript	Grade A (Excellent)
Creativity or innovation of this manuscript	Grade A (Excellent)
Scientific significance of the conclusion in this manuscript	Grade A (Excellent)
Language quality	Grade B (Very good)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	Yes
Does this manuscript report an unconventional innovation?	Yes
Conclusion	Accept
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No

### SPECIFIC COMMENTS TO AUTHORS

The authors have adequately revised the article, and no further comments are noted.