Dear Dr. Jin-Lei Wang:

We would like to thank the editors for giving us a chance to resubmit the paper, and also thank you and the reviewers for giving us highly insightful suggestions which would help us both in English and in depth to improve the quality of the paper. Here we submit a new version of our manuscript entitle " **Novel mutations of the Alström syndrome 1 gene in an infant with dilated cardiomyopathy: a case report**" **(NO:72053)** by Ping Jiang, Liang Xiao, Yuan Guo, Rong Hu, Yi-Bo Zhang, Yi He for consideration of publication in ***World Journal of Clinical Cases*.**

Thank you and the reviewers for carefully reading our manuscript, giving positive comments, and for inviting us to revise the manuscript. As we told you, we treasure this chance very much. We improved our manuscript upon the reviewers and editors' advices. Importantly, we addressed all issues reviewers raised detailed in "**POINT-BY-POINT RESPONSE**".

We hope this revised manuscript is adaptive for publication in ***World Journal of Clinical Cases***. If the manuscript needs further revision, please feel free to contact us and we will be glad to make the work.

Thank you!

Sincerely yours,

The authors.

Response to Reviewer Comments：

Response to Reviewer1#：

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits. Comments: "An interesting addition to the existing knowledge on the genotype of Alström syndrome." We also appreciate your clear and detailed feedback and hope that the explanation has fully addressed all of your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses. To facilitate this discussion, we first retype your comments in italic font and then present our responses to the comments.

POINT-BY-POINT RESPONSE

1. *The authors' statement - // There have been no cases reported with a relationship between DCM and mutation of ALMS1.// is ambiguous. What do the authors try to convey? When cardiomyopathy is an important feature of Alström's, how do the authors say that there has been no case with ALMS1 mutation and DCM?*

Response: Thank you for reminding us the improper description on the study. We agree with the reviewer and editor's suggestion, In the revised paper, the sentence "There have been no cases reported with a relationship between DCM and mutation of ALMS1" have changed to "few interpretations have been made of the related mechanism of the novel ALMS1 gene mutation to induce DCM in infants". We would like to convey that little is known about the mechanism that the *ALMS1* gene mutation can lead to DCM in the infants.

2. *In the case presentation part, the sequence of findings that led to the suspicion of Alström's clinically should be described. This should come prior to the genetic testing part.*

Response: Yes. Your opinions inspired us and we revised the manuscript accordingly. In the revised paper, we described the sequence of findings, the supplementary content is as follows: "Nuclear genomic DNA was extracted from peripheral blood samples of the infant and her parents for amplification with targeted capture of the coding regions

of the genome. Then, amplicons were subjected to whole-exome sequencing by a NextSeq500 sequencer (Illumina, San Diego, CA, USA). Novel genetic mutations in ALMS1 were identified, and genetic analysis showed that the ALMS1 gene (NM_015120) had two mutations on chr2: 73829360 (c.12160C>G, p.R4054G) in exon 20 and chr2: 73827805-73830431 deletion in exons 18–21 (Figure 2). The mutations were confirmed by the Sanger sequencing method, which revealed that c.12160C>G (p.R4054G) and a deletion removing the entire exons 18–21 were acquired by paternal and maternal inheritance, respectively".

3. *In discussion, try to add a few words about the differences between phenotypes (if any) when mutation is found in the hot-spot exons and the non-hotspot exons.*

Response: Your suggestion is greatly appreciated. We agree and therefore we have added a few words that "Variants in non-hotspot exons could result in classical phenotype deficiency or atypical phenotypes, such as the delayed age of obesity and diabetes onset."

Thank you and all the reviewers for the kind advice.

Sincerely yours

The authors

Response to Reviewer2#:

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits. Comments: "The Authors report a novel mutation of the ALMS1 gene causing DCM in a 1-month-old girl. The case is interesting." We also appreciate your clear and detailed feedback and hope that the explanation has fully addressed all of your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses. To facilitate this discussion, we first retype your comments in italic font and then

present our responses to the comments.

POINT-BY-POINT RESPONSE

1. *Medical therapy included Angiotensin converting enzyme inhibitors, spironolactone, digoxin and diuretics. Overall, this therapy seems quite outdated compared to current guidelines on HF (sacubitril/valsartan, betablockers... are not mentioned).*

Response: Thank the reviewer for the comments very much. We've recognized that this description in the previous copy were not accurate, we agree that beta blockers are also optimized therapy, and consideration would be given to replacement of the angiotensin converting enzyme inhibitors with sacubitril valsartan in adults with an ejection fraction below 35% according to consensus clinical management guidelines for Alström syndrome in 2020[1]. So we described the therapy to the sentences: "Both sacubitril/valsartan and dapagliflozin are strongly recommended for adult patients with heart failure with reduced ejection fraction, according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[5], but not in infants, because the safety and efficacy of both have not been confirmed in infants, and further study is needed for evaluation[6,7]. Therefore, drug therapies such as angiotensin-converting enzyme inhibitors, beta blockers, spironolactone, digoxin and diuretics were administered according to consensus clinical management guidelines for AS[1]".

2. *In the manuscript "After standard anti-congestive heart failure treatment, TTE revealed acoustic enhancement in the left ventricular endocardium compared with at admission, which was suspected to have arisen from thickening of the ventricular endocardium as a result of deposition of subendocardial fibrous tissue layers during heart development[8]. Consequently, myocardial fibrosis may also play a role in AS." This concept shoud be removed or toned down, because subendocardial hyperintensity at cardiac ultrasound cannot be used as a surrogate for myocardial fibrosis, which should be demonstrated by the presence of late enhancement at cardiac magnetic resonance.*

Response: Thank you for reminding us the improper description on the study, the reviewer and editor's suggestions have been adopted, the sentences have already been removed.

3. *In the summary the terms "antiventricular remodeling treatment" and "acoustic enhancement in the left ventricular endocardium" are quite unusual and difficult to understand; I would strongly recommend to rephrase this sentence ("heart failure therapy" or "anti-remodeling therapy".... and "subendocardial hyperechogenicity"... respectively, even though this last concept should be removed/rephrased as indicated in point 2).*

Response: Thank you for reminding us the improper description on the study, the reviewer's suggestions have been adopted, we have deleted the last concept in the discussion part of previous manuscript, and the sentence "antiventricular remodeling treatment" was changed to "anti-remodeling therapy"(in the case summary).

4. *There are no biohumoral exams at follow-up (did NTproBNP decrese on medical therapy)?*

Response: Yes. Your opinions inspired us and we revised the manuscript accordingly. In the revised paper, the supplement biohumoral exams have been completed, serum cardiac troponin T (cTnT) level of 0.05ug/L (normal< 0.024 ug/L) at admission, and declined down to normal at follow-up, similarly, Nt-proBNP decreased significantly from 23 681 pg/mL(normal < 125 pg/mL) at admission to 1879 pg/mL at follow up, all of which has been described in the manuscript.

5. *There are no data about the arrhythmic burden; was a 24-holter ECG monitoring performed at baseline and/or at follow-up?*

Response: Yes. Your suggestion is greatly appreciated. In the revised paper, We agree and therefore add the sentences "There were two episodes of paroxysmal atrial tachycardia in 24-hour Holter ECG monitoring, and the maximum heart rate was 180 beats/min, whereas ventricular arrhythmia was not recorded."(during hospitalization,) and the sentence "there was no arrhythmic burden in repeated 24-hour Holter ECG monitoring"(at follow-up).

Thank you and all the reviewers for the kind advice.

Sincerely yours

The authors