World Journal of Clinical Cases

Recurrent acute liver failure associated with novel *SCYL1* mutation: Case report

Dear Editor,

Enclosed please find our revised manuscript entitled "Recurrent acute liver failure associated with novel SCYL1 mutation: Case report" (Manuscript NO: 43213)" for your consideration for publication in *World Journal of Clinical Cases*.

We want to thank the reviewers for careful reading of the manuscript and making detailed suggestions for improvement. Their work is greatly appreciated. We are grateful for the kind assessment provided by Reviewer 2 (Number ID: 03471268) and have taken into consideration the queries posed and comments raised by the Reviewers 1 (Number ID: 03251829) and 3 (Number ID: 03727922). A point-by-point response is supplied. All changes to the manuscript are indicated in the text by highlighting.

We believe that the manuscript is now much improved. We thank the *World Journal* editorial group for allowing resubmission to your forum and look forward to an early decision concerning this revised manuscript. Please let us know if you need further information.

Yours sincerely,

Jian-She Wang

Reviewer reports:

Reviewer #1(Number ID: 03251829): This case report reports a novel homozygous insertion mutation in a patient diagnosed with pediatric recurrent acute liver failure (RALF). The authors have exploited WES to

describe a 7bp insertion (GGGCCCT). The authors claim to expand the clinical mutational spectrum of SCLY1 disease. The authors report the mutation is not reported in datasets such as 1000 genomes, the NHLBI Exome Sequencing Project (ESP) Exome Variant Server (6,500 exomes), or the Exome Aggregation Consortium Browse Comments: -To strengthen their argument they should genotype/confirm the mutation with a PCR assay with allele specific primers and conventional DNA sequencing in both the parents and child. For instance new Scyl1 mutations have been detected by WES and confirmed by PCR in the following publications: EMBO Rep. 2007 Jul;8(7):691-7. Am J Hum Genet. 2015 Dec 3;97(6):855-61. -In page 6 line 27 (Identification of a novel homozygous mutation in SCYL1) the authors should report the exact position of the mutation mentioning the exon or intron of the insertion. -In page 7 line 6 the authors write “The variant appears novel”. The words “appears” denotes uncertainty, is not ideal. They should state “The variant is novel”. -The authors should state if the mutation detected by exome sequencing concurs with Sanger sequencing

Reviewer #2 (Number ID: 03471268): This article revealed mutations of SCYL1 for Chinese patients of RALF with whole exome sequencing. Searching for mutations in minimal cases with neurologic or skeletal abnormalities is rare and may be an aid for future diagnosis. It is the first report in east Asia, and it is considered to be a useful case report.

Reviewer #3 (Number ID: 03727922): The present manuscript entitled " Recurrent acute liver failure associated with novel SCYL1 mutation: Case report" is intreresting. However, I believe that needs improvement in some topics of your manuscript to a better interpretation and to emphasize its importance. Introduction - Clarify the hypothesis stated and the purpouse of the study. Case presentation - Information on approval of a Local Ethical Committee should also be provided in a specific section, if it possible discribe

the number and year. Provide the information on patients informed consent. Should describe clearly the the others ALF treatment? Has genetic evaluation influenced the treatment of the patient? What about costs? Discussion:What were the limitations of your study? What are the real benefits of your study to the clinical and scientific practice? What is the literature regarding this specific evaluation?

Our point-by-point response to this reviewer follows.

Reviewer #1 (Number ID: 03251829):

To strengthen their argument they should genotype/confirm the mutation with a PCR assay with allele specific primers and conventional DNA sequencing in both the parents and child. For instance new Scyl1 mutations have been detected by WES and confirmed by PCR in the following publications: EMBO Rep. 2007 Jul;8(7):691-7. Am J Hum Genet. 2015 Dec 3;97(6):855-61.

Response:

Thank you for your question. Conventional DNA sequencing was indeed performed in the proband, his brother, and his parents. The results were, and are, provided in Supplementary File 2.

In page 6 line 27 (Identification of a novel homozygous mutation in SCYL1) the authors should report the exact position of the mutation mentioning the exon or intron of the insertion.

Response:

Thank you for your comment. We have rewritten the sentence. See page 7, line 4. We also emphasized the exact exon in page 7, line 5, and page 7, line 12.

-In page 7 line 6 the authors write “The variant appears novel”. The words “appears” denotes uncertainty, is not ideal. They should state “The variant is novel”.

Response:

Thank you for your comment. We have rewritten the sentence. See page 7, line 15.

The authors should state if the mutation detected by exome sequencing concurs with Sanger sequencing.

Response:

Thank you for your comment. The mutation detected by exome sequencing concurs with the results of Sanger sequencing. The results of conventional DNA sequencing were, and are, in Supplementary File 2. We have added a sentence that underscores this in page 7, lines 8-10.

Reviewer #3 (Number ID: 03727922):

Introduction

Clarify the hypothesis stated and the purpose of the study.

Response:

Thank you for your comment. We have attempted clarification of these points. See page 4, lines 20-23.

Case presentation

Information on approval of a Local Ethical Committee should also be provided in a specific section, if it possible describe the number and year.

Response:

Thank you for your comment. This information is now included; see page 6,

line 9.

Provide the information on patients informed consent.

Response:

Thank you for your comment. This is addressed on page 6, lines 9-10.

Should describe clearly the others ALF treatment?

Response:

Thank you for your comment. This is gone into now on page 7, lines 21-27.

Has genetic evaluation influenced the treatment of the patient? What about costs?

Response:

Thank you for your question. In our patient, assignment of diagnosis to mutation in a specific gene shifted the context in which we viewed his findings on examination, changing our expectations for the course of what now can be considered as a multisystem disorder. Our care has become better focussed and may perhaps permit orthopedic, physiatric, and neurologic intervention for directed support. We can speak with the patient's family members with greater confidence in what we share with them. In addition, genetic diagnosis can also help prenatal screening. Our revised text now touches on this change, which we see as an improvement in what we can offer our patient and his family. See page 9, lines 27-30 and page 10, lines 1-6.
In respect of costs, even with a genetic diagnosis in hand we are not sure how best to avoid episodes of liver disease — which would certainly spare considerable expense. Less directly, the financial balance between the expense of early intervention and the expense of greater morbidity without such intervention is difficult to assess. The cost of genetic diagnosis *per se*, of course, is gradually falling, allowing us to expect that the ratio of benefit: cost will improve as time passes.

Discussion:

What were the limitations of your study?

Response:

Thank you for your question. Like any case report, our findings are limited in that they are anecdotal and that — with some exceptions — they are open-ended: We can not provide a birth-to-death accounting of *SCYL1* disease in our patient, so that our report is, by the highest standards, incomplete. Thus if other caregivers draw on our experience as reported here, they must do so cautiously. In unusual disorders like *SCYL1* disease, however, it is case reports — particularly ones like ours, that describe patients with clinical pictures that vary from general consensus — that must shed some light and provide some guidance. We are grateful to the editors of Baishideng Publishing Group and to the reviewer for seeing value in such reports and we hope that they will continue to do so. Our revised text now mentions this inherent deficiency. See page 10, lines 14-15.

What are the real benefits of your study to the clinical and scientific practice?

Response:

Thank you for your question. If our study is taken up by caregivers, we anticipate that delay in diagnosis of *SCYL1* disease may be lessened in patients whose presentation, or whose constellation of abnormalities, varies from that usually considered typical for *SCYL1* mutation. More speedy diagnosis should permit earlier and better-directed intervention on behalf of patients (see above) and, indeed, in their family members (as with genetic counselling). Our revised text now proposes this as a useful benefit of knowing more about "atypical" *SCYL1* disease. See page 10, lines 15-17.

What is the literature regarding this specific evaluation?

Response:

Thank you for your question. Based on a search of the databases available to us, we believe that our manuscript incorporates by reference what is at present known about the disorder and about how to assess it clinically and genetically, including an update (page 4, lines 18-19 and page 8, lines 21-22) citing work not yet published when an earlier version of the manuscript was submitted to *World J Gastroenterol*. We shall be truly grateful if you kindly point out to us any deficiencies in this respect of which you are aware.