Author’s response to reviews

Title: Identification of a novel nonsense mutation in SH2D1A gene from a patient with X-linked lymphoproliferative syndrom type 1: a case report

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POINT-BY-POINT RESPONSE

Laura S. Schmidt (Reviewer 1):

Lyu and colleagues describe a case of an 18 month old male patient with a novel nonsense mutation in SH2D1A and a diagnosis of XLP1. They show that the mutation results in a truncated mRNA and suggest this causes the production of a non-functional protein. They demonstrate that the mutation was inherited from the patient's mother.

1) pg 7, line 29-30: use of "might be pathogenic" suggests that pathogenicity is not confirmed. However, nonsense mutations typically are considered "likely pathogenic" since they truncate the protein, so this would be a better choice of wording here.

Answer: We had changed the word and use "likely pathogenic" to describe the mutation more appropriately.

2) Fig 3: patient is hemizygous not homozygous for mutation. Also symbols on pedigree need to be defined in legend (white symbol with dot, arrow indicates proband, etc.)

Answer: Thank you for your attentive correction. We had correct the error of zygosity in the figure legend. We also defined all symbols in the legend.
3) A truncated SH2D1A mRNA may still produce a truncated protein that could have partial function. It would be informative to perform Western analysis of the mutant SAP protein to determine if it is produced and stable or unstable. In addition, if a stable truncated protein is produced, the authors should discuss the potential consequence of a c-terminally truncated SAP protein based on knowledge of its function and the importance of the c-terminus to function, if this is known.

Answer: To address this question, we had included two previous studies (ref 9 and 10) focused on structures and function of SH2 domain in SAP protein, in the second paragraph of Discussion Section. These studies showed that mutations occur within the βG strand and boundaries of the SH2 domain of this protein could directly implicate the SH2 domain in the pathogenesis of XLP. The mutation we reported here occurs just in this area.

Marta Olszewska, Ph.D., M.Sc. Eng. (Reviewer 2):

Dear Authors,

your manuscript is interesting and can be published after some minor points:

1. English correction should be done by native speaker. In the manuscript, there are some strange grammar constructions that are not English. Additionally, some sentences are too long and need to be cutted into 2-3 shorter ones, to give better flow of reading. Also, some commas are missing. Some suggestions are presented in an attachment.

Answer: Thanks a lot for your earnest suggestions. We had asked for help from a professional agency. The manuscript had been revised by a native speaker. We hope that it is now suitable for publication.

2. Negative control should be explained in a paragraph with RT-PCR description.

Answer: The control sample and its PCR result had been described in the revised manuscript.

3. Conclusions should be more directed into the fact, that you have found a novel mutation, rather (or simultaneously) that the apli-seq method role.

Answer: The conclusion section had been revised according to this suggestion.
4. Some legend should be included into Figures' description.

Answer: All arrows and symbols had been defined in the legend.