Author’s response to reviews

Title: Mutations in the PIGW gene associated with hyperphosphatasia and mental retardation syndrome: a case report

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Technical Comments
1. CARE Guidelines:
Case reports submitted to the journal must have a populated CARE checklist included as an additional file
reply:The populated CARE checklist has been included as a supplementary file.

2. Figure legend:
The legend and title should be part of the manuscript file, given after the reference list.
reply:We have given the legend and title after the references list in accordance with the requirements.

Editor Comments
Reviewer #1: Fu et al. report a new case of Hyperphosphatasia with mental retardation syndrome (HPMRS) related to mutations in the PIGW gene.
1. The report of this case could be the opportunity to make a review on HPRMS and share knowledge on this group of pathologies with the readers of BMC pediatrics. Unfortunately, there are some mistakes and omissions in the paper that make it difficult to be published without major revisions.

Background: HPMRS may be caused by PIGV, PIGW, PIGO, and PGAP2, as described by the authors but also by PIGL (Fujiwara et al. Mutations in PIGL in a patient with Mabry syndrome, Am J Med Genet A. 2015;167A:777-85), PIGY (Ilkovskiet al. Mutations in PIGY: expanding the phenotype of inherited glycosylphosphatidylinositol deficiencies, Hum Mol Genet. 2015;24:6146-59) and PGAP3 (Howard et al., Mutations in PGAP3 impair GPI-anchor maturation, causing a subtype of hyperphosphatasia with mental retardation, Am J Hum Genet. 2014;94:278-87) mutations.

Moreover, two articles reporting PIGW mutations, and not only one, have been published "Hogrebe et al., A novel mutation in PIGW causes glycosylphosphatidylinositol deficiency without hyperphosphatasia, Am J Med Genet A. 2016;170:3319-3322 must be added.

reply: Thanks for the reviewer. We supplemented some information about the mutations by PIGL, PIGY, and PGAP3 in the background. And we also added the article "A novel mutation in PIGW causes glycosylphosphatidylinositol deficiency without hyperphosphatasia", Am J Med Genet A. 2016;170:3319-3322.

2. Case presentation:

Page 2, Ligne 45: please change "AKP" to "alkaline phosphatase (ALP)"

Because of the renal or cardiac malformations that are present in some HPMRS patients, it could be relevant to indicate the status of the patient regarding these organs.

reply: Thank you very much for your advice. We have changed "AKP" to "ALP" in this manuscript. The patient's renal function (we inspected by creatinine clearance rate) and myocardia enzymes were normal. And we have supplied in the case presentation.

Page 3, ligne 6: "psychomotor retardation" could be more relevant than "mental retardation".

reply: Thank you very much for your advice. We have changed "mental retardation" to "psychomotor retardation" in the manuscript.
3. Gene mutation analysis:

Page 3 ligne 40: please change "mutations" to "variants".

reply: Thank you very much for your advice. We have changed "mutation" to "variants" in the manuscript.

Moreover, it is necessary to discuss the possible pathogenicity of the variants (predicted pathogenicity by softwares of prediction, known or not in polymorphisms database, position in the protein, etc…), which are "of uncertain significance", like noticed in the supplemental data.

reply: Thank you very much for your advice. We performed the functional prediction by the software, Polyphen 2, and the mutations are predicted to be probably damaging. We had added the details in the part of "Gene mutation analysis".

Since the pathogenicity is uncertain (although the reviewer thinks that the variants are pathogenic, it is important to demonstrate it), a study of GPI-anchored proteins by quantification with multiparameter flow cytometry should be done in the patient (a low level is expected in the patient).

reply: Thank you very much for your advice. However, it is regretful for us not to complete the functional studies to assess the effects of the variants on the protein. We didn't preserve the blood sample of the patient in the follow-up and the patient died in October, 2017 because of the serious pneumonia.

Page 3 ligne 47: the legends of the figure seem to be at the wrong place in the article?

reply: Thank you very much for your advice. We have changed the legends of the figure at the right place which is after the reference.

4. Discussion:

Page 4 ligne 24: same comment than for background (genes involved in HPMRS)

reply: Thank you very much for your advice. We have added the related contents in the discussion.
Page 5 ligne 19: the level of alkaline phosphatase should be indicated in the case presentation section, not in the discussion.

reply: Thank you very much for your advice. We indicated the level of alkaline phosphatase in the case presentation section, and deleted the related content in the discussion.

Page 5 ligne 23: the pulmonary disease of the patient should be a little more discussed. The brother had the same respiratory phenotype; what about the other patients in the literature? Never reported?

reply: Thank you very much for your advice. We have discussed the pulmonary disease of the patient more in the discussion section. And there is one literature mentioned the patient died from aspiration. And we thought it may be aspiration pneumonia, because it was not specified clearly in the literature. We have given the description in detail in the article.

Bibliography: in addition to lacking reference, there are some typographic mistakes (lack of spaces between words, place of surname for example in ref1), a reference is duplicated (Krawitz 2010, ref 6 and 14) and the numbers in the text are not related to the good article (for example ref 13 is not about PIGW).

reply: Thank you very much for your advice. We are very sorry for the careless and we have rearranged and modified the references in the article.

Supplemental data: Unfortunately, the reviewer could not judge if the data are relevant since the text is in characters that he is not able to understand.

reply: Thank you very much for your advice. We have uploaded them again.

Reviewer #2: The manuscript reports the identification of a compound hit in the PIGW gene and links this finding to the phenotype HPMRS. The manuscript is easily understandable but some points need to be clarified:

- The variants identified in the present study should be described more in depth. Some databases have been used for filtering, according to these databases, what is the description of the variants: frequency in the general population, pathogenicity...

reply: Thank you very much for your advice. None of the above variants were polymorphic and it occurred very infrequently in the population (The reference database: 1000Genomes,
dbSNP). We had the functional prediction by the software, Polyphen 2, and the mutations are predicted to be probably damaging. We had added the details in the part of "Gene mutation analysis".

- They should also been compared to the previous reported variants.

reply: Thank you very much for your advice. We have added the contents compared to the previous reported variants in the discussion selection.

- There is also a lack of functional studies to assess the effects of the variants on the protein. They were performed in the study of Hogrebe et al: Transfection of the mutated allele into Pigw-defective CHO cells indicated impaired enzymatic activity of the mutated PIGW product. Is it possible to realize the same kind of analyses?

reply: Thank you very much for your advice. It is a pity for us that the functional studies donot performed to assess the effects of the variants on the protein. We did't preserve the blood sample of the patient in the follow-up and the patient died in October, 2017 because of the serious pneumonia.

- The feature "mental retardation" is not suitable for a 70 day old baby: the author should use psychomotor retardation at this age or intellectual deficiency later.

reply: Thank you very much for your advice. We have changed "mental retardation" to "psychomotor retardation" in the manuscript.