Author’s response to reviews

Title: A de novo ANK1 mutation associated to hereditary spherocytosis: a case report

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Version: 2 Date: 21 Dec 2018

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Editor Comments:

Thank you for reducing overlap with the Guan et al study. However, there remains some overlapping sentences and we ask that you edit where possible to further reduce this (please see that attached screenshot for some examples).

Answer: Thanks for the suggestion. We had revised it.
Reviewer 1

1. Line 25: It would be better if the statement that HS has 'few clinical manifestations' be changed suitably to highlight the unique manifestations of HS in the neonate and infant.

Answer: Thanks for the suggestion. We had changed it.

2. OFT is well known to be fallacious in HS. Did the authors perform EMA binding as recommended in the recent BCSH guidelines?

Answer: Thanks for the suggestion. But we didn't done EMA binding tests.

3. It is well known that in infants, the diagnosis of HS is difficult. The neonatal HS ratio is often useful to guide the diagnostic algorithm. In the index infant, the ratio was >0.36, which points towards a diagnosis of HS. It will be more clinically relevant if the authors discuss the unique clinical and laboratory manifestations, including the diagnostic challenges of HS, specific to the neonatal period and infancy.

Answer: Thanks for the suggestion. We had explained it in background.

4. Sequencing is useful in difficult hemolytic anemias after a complete diagnostic workup has failed to yield a diagnosis. I think that in the index case, there was an opportunity to diagnose by conventional methods. Even if not possible at 3-4 months, often the diagnosis becomes quite evident as the infant grows a bit older. As sequencing, though useful, is not easily available to all, the authors may chose to be prudent and highlight that a wait-and-watch approach may also be appropriate, especially in resource-limited settings and sequencing may be useful only if the conventional algorithm does not yield a diagnosis once the child is 8-10 months old.

Answer: Thanks for the suggestion. We had explained it in discussion.

5. The authors stress on the absence of family history; however, this is a well-known phenomenon in many countries. A contributory family history is more likely in the Western population, but is often infrequent in many studies in the East. The authors may choose to mention this.

Answer: Thanks for the suggestion. We had explained it in discussion.
6. The triad of HS is rarely found in infants. Transfusion requirement in infancy is not predictive of severity of disease in later life, as there is often a component of hypoproliferation, which requires transfusions and sometimes even EPO to restrict transfusions, in addition to folic acid. It would be interesting to know the subsequent clinical course in this child and the authors may seek to highlight this. This would provide a more practical and educational clinical perspective. The word limit can be managed by omitting several repetitions.

Answer: Thanks for the suggestion. We had highlighted the clinical course in case presentation and omitted the repetition.

7. Lines 80 and 128: Please change from "liver-splenomegaly' to the more conventionally used terminology, 'Hepatosplenomegaly.'

Answer: Thanks. We have made the revision as the suggestion.

8. Line 35: Please omit the term 'first report' and just mention that this is a novel mutation.

Answer: Thanks. We have revised it.

Susana Rocha (Reviewer 2): General considerations:

The subject matter of this work is well within the scope of the BMC Pediatrics Journal and it is a very to the point, clear-cut paper as any case report should be.

The novelty of the work is to present a new mutation underlying HS, proving further knowledge about the physiopathology of this hereditary disease.

Specific considerations:

In the overall text, the authors present the expression "de novo" without being in italic in several instances. As is it a Latin expression, it should be denoted differently from the rest of the text (in English).

Answer: Thanks. We have revised it.

Line 1 - In my opinion, "risk factor" is something that increases predisposition or susceptibility of developing a disease, such as, a habit or an environmental condition. A mutation is something
that is intrinsic to the individual thus calling it a risk factor is a bit exaggerated. I suggest changing the title to "… mutation underlies a new case of …" or "… mutation associated to…"

Answer: Thanks. We have made the revision in the title.

Lines 39 and 143 - What do the authors mean by "intractable"? Are they saying that some hemolytic anemias are difficult to diagnose by routine means or do they mean that these HA are not possible to be cured, as they are hereditary diseases? The authors should rephrase the sentence to be better understood.

Answer: Thanks. We have made the revision.

Lines 50-51 - As Band 3 is more common name for the protein encoded by the "SLC4A1" gene and it is usually what is described in HS articles, the authors should add "or Band 3" after "soluble carrier family 4, number 1".

Answer: Thanks. We have made the revision.

Line 76 - Because blood transfusions can adulterate the analytic results it should be specified that the routine blood examinations were performed before the transfusion (if it was the case, as I believe so).

Answer: Thanks. We have made the revision.

Lines 104-105 and 155 - RBCs acronym is widely used to refer to "red blood cells" and not "spherical-shaped blood cells". As it can cause confusion, I urge the authors to choose another abbreviation

Answer: Thanks. We have made the revision.

Line 108 - delete "all"

Answer: Thanks. We have made the revision.

Line 121 - delete "ankyrin"

Answer: Thanks. We have made the revision.

Line 140 - substitute "database" by "databases"

Answer: Thanks. We have made the revision.

Line 232 - substitute "2018:1-4" by "2018; 23:413-16"

Answer: Thanks. We have made the revision.
Line 245 - substitute "Spherocytosis are indicated by an arrow" by "Spherocytes are indicated by arrows"

Answer: Thanks. We have made the revision.

Line 247 - substitute "HS" by "gene mutation"

Answer: Thanks. We have made the revision.

Line 248 - substitute "indicated" by "indicates"

Answer: Thanks. We have made the revision.

Line 249 - Change to the title of the table to something similar to "Laboratory test results of the patient at time of birth" and RBC value is within the reference range, so the arrow should be deleted.

Answer: Thanks. We have made a revision. As shown in the table 1.

Line 255 - Change to the title of the table to something similar to "Laboratory test results of the patient at eleven months of age"

Answer: Thanks. We have made a revision. As shown in the table 2.

Line 258 - substitute "G-6PD" by "G-6-PD"; also, in the table.

Answer: Thanks. We have made a revision. As shown in the table 2.