Author’s response to reviews

Title: A novel missense mutation in the MYH7 gene causes an uncharacteristic phenotype of myosin storage myopathy: a case report

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Author’s response to reviews:

Dear Editor,

Thank you for your favorable decision for this article for publication, with minor corrections.

All changed requested by reviewers have been made.

As regards of language editing, we prefer to proceed in 2 steps. In order to avoid confusion about the content, in a first step we prefer to send you a version with all the changes. Thereafter, we’ll make the language editing and then send to you the final version.

Please see below, in the next pages, the answers/replies/comments to the reviewer’s comments.

Also, additional changes have been made as follow:

- Title page, line 23

The corresponding author has been changed. In order to receive correspondence directly so that we can treat information quickly, JM acted as corresponding author during submission process. However, all correspondence after the publication of this article should be sent to Dr Alier Marrero, which is the neurologist involved in this case, in close contact with all the co-authors.

- Reference (Page 10)
Given the fact that we added 1 reference within the text (Page 6, Line 13, reference [9]) the previous numbering has been changed. The cited reference has been added to the list.

- Abbreviations (Page 8, lines 20-21)

Abbreviations for ACMG and AMP, cited within the text (Page 6, Lines 11-12) have been added.

Best regards,

Jean Mamelona

Current corresponding author

Craig Kinnear (Reviewer 1):

1) Please provide some more information about the way that the variants were filtered and prioritized following exome sequencing.

Additional information about the way that the variants were filtered and prioritized following exome sequencing has been included in the text: Page 5, lines 12-22. (The genomic DNA was extracted …/… to an external laboratory for Sanger sequencing).

2) The variant is classified as likely pathogenic by the authors following results obtained from VarSome. Does this hold true if one applies the recommended guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Genet Med. 2015 May ; 17(5): 405-424. doi:10.1038/gim.2015.30.)? Please use these guidelines to classify the variant.

Yes, this hold true when using ACMG and AMP. Additional information about the results has been included in the text: Page 6, lines 11-13. (Also, the results of analyses … and 2 supporting (PP2 and PP3) [9]).
The reference cited for this portion of text has been added in reference list and the numbering within the text and in the reference list has been changed accordingly.

3) I have noted that the necessary controls were not included. In order to confirm that this variant is disease-associated, one should be able to show that it segregates within the family, I do accept that this was not possible due to the lack of clinical information and genetic material available for the index case’s relatives.

We totally agree.

It would be very useful to have DNA test results for the parents of the index case. Unfortunately, as we mention this in the article this was not possible. As you probably do think the same, considering the circumstances, we suggest that this mutation comes into support to the clinical findings despite the lack of results of segregation analyses.

4) The manuscript contains a number of grammatical errors that needs to be addresses.

To avoid confusion about the content we prefer to send you first the same version with all the change being made directly on the text. Please, let us know once reviewers finished checking our replies/comments, and then we’ll work on language editing.

Shantel Weinsheimer (Reviewer 2):

1) There is no formal methods section that describes the details of the immunostaining experiments (e.g. antibody details), also there seems to be no control presented for the immunostaining experiment. There are no methods to describe the whole exome sequencing and Sanger sequencing experimental details. A small methods section could be added to present this information.

Additional information about the formal methods section that describes the details of the immunostaining experiments has been included in the text: Page 4, lines 21-26. (Immunohistochemical detection of p62 …/… and the Hematoxylin counterstaining solutions).
Information about whole exome sequencing and Sanger sequencing experimental details has been included in the text: Page 5, lines 12-22.

(The genomic DNA was extracted …/… to an external laboratory for Sanger sequencing).

2) The authors could consider including a sentence before the presentation of the WES results to introduce why genetic testing was pursued.

A sentence introducing why genetic testing was pursued was included in the text: Page 5, lines 11-12.

(The blood samples were collected for… observed for this patient.)

The authors did not describe whether there were any other variants in other genes identified in the WES experiment that were potentially harmful. If none present, then a statement about this could be included in this manuscript.

You’re right. It’s important to mention if there were another variants detected.

Indeed, two others potentially deleterious variants were detected. However, both mutations potentially affect proteins that do not play role in neuromuscular function. Information about this has been added in the text: Page 5 line 26 - page 6 line 3.

(Two other candidate mutations were …/… of neuromuscular disorders observed for this patient.)

3) It would be nice if there was a statement that described why the p62 marker was chosen for the immunostaining experiments to identify the intrasarcoplasmic inclusion bodies.

A sentence explaining the choice for the immunostaining experiments has been added in the text: Page 4, lines 19-21.

(Given we could not… the presence of inclusion bodies.)
4) There are a few grammatical errors that need to be corrected.

We agree that therefore the text needs a language editing.

Please refer to our reply 4 for the reviewer 1 (see above).