Reviewer’s report

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

Version: 0 Date: 18 Dec 2018

Reviewer: Shantel Weinsheimer

Reviewer's report:

Reviewer comments:

Mamelona et al. presents a clear case report of a 41 year old woman who had childhood onset of muscular disorder that progressed during her thirties and worsened in her early forties to include involvement of skeletal, respiratory and cardiac muscles, such that she has become severely incapacitated. Her clinical myopathic features suggested myosin storage myopathy and indication of protein aggregation disease.

Whole exome sequencing followed by Sanger sequencing confirmed that the woman has a novel missense variant in the MYH7 gene that leads to a single amino acid change (Ile -> Arg) in the head motor domain of the slow/cardiac beta myosin heavy chain (MyHCl). Bioinformatics analyses suggest this variant is likely pathogenic with potentially damaging impact on protein structure. Hence, the authors propose the change potentially impairs electrostatic amino acid interactions which might destabilize the beta strand structure.

Additionally, previously published functional studies suggest that mutations within this cleft of the myosin motor domain may result in dysfunctional myosins. The authors suggest in the discussion that this mutation could become additively deleterious when the myosin molecules form the thick filament which would affect the organization and performance of the sarcomere. Taken together, this evidence suggests that this variant could contribute to the phenotype of muscular disorder observed in this patient. The authors conclude this is the first case linking mutation in the motor domain of MyHCl to myosin storage myopathy.

While this is a well written manuscript there are a few points for consideration:

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.

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

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.

4) There are a few grammatical errors that need to be corrected.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published
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