Author's response to reviews

Title: Compound heterozygosity of predicted loss-of-function DES variants in a family with recessive desminopathy

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Author's response to reviews:

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To the BMC Medical Genetics Editorial Team:

Enclosed, please find a revised case report titled “Compound heterozygosity of predicted loss-of-function DES variants in a family with recessive desminopathy,” by McLaughlin, et al. (MS: 1548255209877362). We thank the reviewers for their positive feedback and constructive comments, and we are excited about the potential to publish our case report in BMC Medical Genetics. You can find our detailed responses to the reviewer’s comments below in bold.

Reviewer: Denis Duboc

The method and the results are of interest. (The clinical report is clearly presented). Some reference concerning the autosomal recessive inheritance are lacking and could improve the quality of the discussion which is the major interest of the case report. Recent review published in Jan 2013 (or other) on mechanism and pathology of desminopathies could be helpful.

We agree that adding the recent description of a family with an autosomal recessive desminopathy would be a valuable addition to this case report. We have now included this information in the discussion.

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Reviewer: Anna Kaminska

Major Compulsory Revisions
The authors describe a case of severe early-onset skeletal myopathy, dilated cardiomyopathy, and respiratory dysfunction in a patient with recessive desminopathy. The condition is extremely rare. Only two cases of such desminopathy exhibiting a recessive mode of inheritance have been reported to date. This report broadens the spectrum of desminopathies and provides new informations both on the molecular mechanisms of desminopathies and its clinical phenotype.

However, there is some imprecision and omissions in the clinical description of the proband. For example, no information is given about the current neurological status of the patient.

We apologize for this oversight and have now provided comprehensive clinical information, including a more detailed description of the patient’s current neurological status.

It is mentioned that Botox injections for tight heel cords at age 14? ultimately resulted in loss of ambulation? which I would contend is unlikely. The next sentence continues ?her muscle wasting has progressed, and she now requires an automated wheelchair with neck support?

We have revised the sentence about the Botox leading to non-ambulation and the above additional neurological assessments should address the remainder of this concern.

Are the facial muscles involved (the younger brother ?was also reported to have floppy eyelids?)? No information is given on the distribution of muscle weakness.

We have included this information in the revised clinical history.

I believe that some clinical photographs may add some clarity to the description.

Unfortunately, we were not given consent to publish photographs of the proband or her deceased brother.

It is difficult for me to understand that the patient neither underwent electromyography nor had muscle biopsy to confirm the skeletal myopathy.
A biopsy was previously performed on the proband’s brother, and the results are now summarized in the Case Presentation. The proband’s parents elected not to have a biopsy performed, as they felt the information obtained from the brother’s muscle biopsy was sufficiently informative in her case.

It goes without saying, detailed clinical information is necessary to better characterize the phenotype of this rare disease. In summary- the part ?Case presentation? has to be re-written. It should include relevant positive and negative findings of the patient?s history, examination and investigation.

We have revised the Case Presentation section to provide an extensive description of the patient’s phenotype.

Minor Essential Revisions

As for the genetic part the authors could more rigorously substantiate their clam about the causative influence of both mutations. For instance they could provide an analysis of DES transcripts, to show stable, truncated DES mRNA, together with full-length mRNA. They could also show at the protein level the presence of both normal and truncated DES polypeptide forms.

We agree that more evidence is needed to definitively state whether the variants identified in our case report lead to loss-of-function, however if these variants are true loss-of-function variants, we would not expect to see either stable truncated DES mRNA nor any full length DES mRNA as all mRNA species would be expected to undergo NMD. This would also lead to a lack of detectable DES protein.

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Reviewer: Hans Goebel

Under "Case presentation" it is mentioned that the molecularly identically affected deceased brother had a muscle biopsy while the patient reported here apparently had not. In view of the compound heterozygozity affecting both desmin genes I wonder whether any desmin was expressed and, perhaps with other proteins, aggregated in the brother’s biopsy specimen. This can easily be checked by immunohistochemistzry and/or Western blot.
We agree that staining the deceased brother’s muscle biopsy sample for desmin would add valuable information to our case report. However, while we were given permission to perform molecular genetic testing on DNA obtained from this sample, consent was not obtained to perform any staining of the muscle biopsy.

Three minor points.

1. Under "Background", line 11: "..variants have been reported..."
2. The paragraph before "Discussion" actually is part of the discussion.
3. Is ref. 9 a one page article?

1. We have edited line 11 of the background and we thank the reviewer for notifying us of this grammatical error.

2. The paragraph before the discussion is not a discussion, but a clinical evaluation and interpretation of the variants identified. We therefore chose to include this section in the results section.

3. Reference 9 is a 10 page article, and was correctly cited as:


In light of the enthusiastic comments from the reviewers and the improvements we have made herein, we hope that you will find our case report suitable for publication in BMC Medical Genetics. Thank you for your consideration, and we look forward to hearing from you.

Sincerely,

Jonathan Picker, MBChB, Ph.D. on behalf of the authors.