Author’s response to reviews

Title: A case report of recessive restrictive cardiomyopathy caused by a novel mutation in cardiac troponin I (TNNI3)

Authors:

Malena Pantou (pantou@ocsc.gr)

Polyxeni Gourzi (gourzi@ocsc.gr)

Aggeliki Gkouziouta (agkouziouta@yahoo.gr)

Iakovos Armenis (iakovosarm@hotmail.com)

Loukas Kaklamanis (loukasgka@yahoo.gr)

Christianna Zygouri (christianna_@hotmail.com)

Pantelis Constantoulakis (pconstantoulakis@genotypos.gr)

Stamatis Adamopoulos (stamatis.adamo@gmail.com)

Dimitrios Degiannis (degianis@ocsc.gr)

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Author’s response to reviews:

Dear Editor,

Thank you very much for your letter of February 13, 2019, in which you include the comments of the reviewers, which we found to be constructive and fair.

We have made the appropriate changes in our manuscript and here is a detailed description of the amendments that have been done according to reviewers' comments.

(Reviewer 1)

Regarding his first comment on the hypothesis as to why this mutation compared to others located in the same or nearby residues seems to act in a recessive way we have added a sentence in the discussion (p. 9, lines 5-10).

Regarding his second comment an addition has been made to the discussion (p.9, lines 10-15).
(Reviewer 2)

Discussion has been expanded and now comprises a section (p.8, lines 1-5) where we present data on the functional importance of the specific region and propose its characterization as mutational hotspot.

The misalignment has been corrected in figure 1A and now the zygosity of the twins is stated in figure 1 legend (p. 15, line 2).

(Reviewer 3)

Reviewer 3 has a similar proposal to Reviewer 1 over the recessive nature of this novel mutation compared to others located in the same or nearby residues. To provide a possible explanation we have added a piece of text in the discussion section (p. 9, lines 5-10)

(Reviewer 4)

Corresponding the clinical data we have made the following amendments following the reviewer's suggestion point-by-point:

- For the index case, symptom (dyspnea) duration has been clarified (p.4, line 7), while a previous stroke and paroxysmal atrial fibrillation have already been stated. Moreover, AF management and evolution has been clarified in the text (p.4, lines 7-9, lines 17-19).

- The term “appropriate treatment” has been substituted by the exact treatment regimen both at first presentation (p.4, lines 8-9) and before clinical deterioration (p.4, lines 18-19). Moreover, treatment regiments of all family members have been included in Table 1.

- Serial echo studies have not been included in table 1, in order to avoid extreme complexity and repetition of similar values. Instead, echocardiographic differentiations occurring during follow-up have been included in the text (p.4: lines 12-14, 21-23; p.5: lines 8-17, 24-25; p.6: lines 1-4). Parameters/measurements not clearly stated in the revised form remained substantially unchanged.

- In Table 1, both age of investigation and current age have been included. Body dimensions in the form of height and body surface area (BSA) have been inserted for all family members and normal range for measurements has been included in brackets. Normal values have been exported from appropriate references (Lang et al, 2015-Pmid 25559473, Caballero et al, 2015-Pmid 25896355, www.parameterz.com). For the brother, no LVOT obstruction has been detected and this has been clarified in the revised form of the text (p.6, line 3-4).

- The diastolic doppler parameters have been explained in table 1 and especially in the text (p.4, lines 12-14, p.5, lines 11-13, lines 15-17, p.6, line 2), together with their clinical interpretation (differentiation between HCM and RCM).
-Body height and Body surface area have been included in Table 1 in a separate column.

-Right heart catheterization results have been rewritten (p.4, lines 15-17; p. 5, lines 17-18) in a more understandable way omitting irrelevant or difficult-to-understand data, however they cannot be fully excluded, as diagnosis and differential diagnosis lie on them.

Corresponding the genetic data we have made the following amendments following the reviewer's suggestion point-by-point:

-In Figure 1 and in the pedigree the relationship of the parents to each other (third cousins) has been indicated and the pedigree has been expanded to include generation III. The pedigree expansion has been also stated in the case presentation section (p.6, lines 11-15). We could not expand the pedigree towards previous generations as we have no data on the antecedents of generation I.

-pedigree symbols have been modified to include only phenotype and genotype is now indicated by +/-.

-The ACMG criteria along with the corresponding codes that this variant fulfills are stated in the Genetics analysis section (p.7, lines 6, 8, 11-14).

- The twins are dizygotic and this is stated in the pedigree.

-A figure of the histology of the native heart has been added as Figure 2 and a corresponding description has been added in the case presentation of the proband (p.5, lines 2-4). We could not procure protein expression of troponin I and immunofluorescent localization as the pathology lab did not have the corresponding antibody to perform the experiment.

We believe that the suggested corrections and additions have improved considerably our manuscript. We want to thank you personally, and the reviewers, for the time and effort dedicated in reviewing our manuscript and we will be honored if you find it acceptable for publication in BMC Medical Genetics in its revised form.

Sincerely yours,

Polyxeni Gourzi, PhD