Reviewer’s report

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

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Reviewer: Brenda Gerull

Reviewer’s report:

Pantou et al. describe a family with a novel TNNI3 variant p.(Asp196His) which leads in homozygous state to a phenotype of restrictive or hypertrophic cardiomyopathy. Heterozygous carrier at an advanced age do not show a phenotype of cardiomyopathy. They conclude that this variant follows a recessive mode of inheritance.

Overall, mutations in TNNI3 are a known cause of all types of cardiomyopathies including RCM and HCM. Even transitional forms between both forms are known for the same mutations. Recessive disease for TNNI3 mutations has been described for DCM and HCM, usually in children and with a severe, early onset phenotype. The case here seems interesting because of their unusual mild presentation of a RCM like phenotype at a homozygous state at a relatively old age of the proband. In addition, the sister and the brother have even less severe clinical presentations. Also, mutations at the same residue have been shown dominant phenotypes before, which may indicate that this novel variant is less pathogenic or part of the phenotypic spectrum/heterogeneity and may also cause disease in a dominant state.

There are few concerns which needed to be addressed:

Clinical data:

- for the index case I am missing prior medical or symptom history before the first presentation at the age of 41 years

- what means "appropriate treatment“ at line 13 page 4; treatment could be also included in table 1 of all affected probands

- serial investigations of affected cases (echo) should be included in Table 1

- Table1: age of investigation should be indicated rather than the current age; as indicated above f/u data on the index case, the sister and the brother should be included; for the brother a septum of 12mm is suggested as HCM phenotype, which could be depending on body height still in a normal range, how about LVOT obstruction; please put all reference values in brackets, also the diastolic parameters are not explained at all (E:A; E/A; DT);
- in addition the diastolic parameters should be explained more general in the text as they are important for the discrimination between HCM and RCM.

- reference values according to echo guidelines should be used (Lang et al. Eur Heart J Cardiovasc Imaging. 2015;16:233-70. and Nagueh et al. J Am Soc Echocardiogr. 2016;29:277-314) or at least an index according to body height (diameter) or body surface area (volumes) should be included in the table

- the clinical information described in the text sounds very "hemodynamical" and "technical", which is for a general reader of a genetic journal difficult to understand. It should be more focused on the specific cardiomyopathy phenotype (e.g. exclusion of coronary artery disease is irrelevant) and clearly outline their specific characteristics

Genetic data:

- please indicate in the pedigree the relationship of the parents to each other (third cousins) and expand the pedigree to more generations

- pedigree symbols should only show the phenotype and not both mixed genotype and phenotype; the genotype may be indicated by +/- or so

- it states that the variant is classified as "likely pathogenic" according to ACMG criteria; please indicate why is it not a VUS?

- are the twins monozygotic twins? if so the different presentation of the phenotype severity would be even more interesting as environmental factors are more likely modifying the disease expression; should be easy to find out

- the index case underwent heart transplantation, there should be heart tissue of the heart explant; is there any histology available showing the restrictive cardiomyopathy, even protein expression of troponin I and immunofluorescent localization would be very interesting to see

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

Yes

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

Unable to assess

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:

Acceptable

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