Reviewer’s report

Title: Non-Familial Cardiomyopathies in Lebanon: Exome Sequencing Results for Five Idiopathic Cases

Version: 0 Date: 08 Jul 2018

Reviewer: Hane Lee

Reviewer’s report:

Refaat et al. describes exome sequencing results on 6 cases clinically diagnosed with various forms of cardiomyopathies. They claim this is the first exome sequencing study done for cardiomyopathy in Lebanon and propose that the study supports the need of systematic genetic testing for this patient cohort for better clinical management.

Major concerns

1. Variant filtering process and results are not clear and sounds like some of the patients who had 'pathogenic' findings in one of the 85 genes didn't really get a full exome analysis.
   a. Were variants called with a target-interval? If so, please specify
   b. A (supplementary) table should be added to show for 'each' sample the exact number of variants identified: 1) total, 2) within coding region (is it coding region or variants with coding changes in page 5 line 7? If only 8500 SNVs and 450 Indels were identified in the coding region, that's concerning as it's only ~half the number of variants typically identified in exome coding region), 3) with minor allele frequency <X% (for rare variants and 5% seem too high even for cardiomyopathy), 4) within 85 known genes
   c. I would actually suggest that after filtering out common variants (>1%), authors count all 'homozygous', 'potential compound heterozygous' and 'heterozygous' variants before intersecting with the 85 known genes
   d. I would also suggest for the heterozygous variants, keep the missense variants in genes with ExAC missense Z-score >3 in addition to the loss of function variants.
   e. Reporting all variants in 85 known genes in the tables seem unnecessary. Only the rare variants should be reported and should include more information like population allele frequency, clinvar/HGMD classification, ExAC missense/LoF Z-score/pLI, etc that could help the variant interpretation and classification. Variant classification base on the ACMG guideline can be added too.
2. Patients MR38 and MR22 seem to have additional features than cardiomyopathy and seem not such a great fit for this study. MR38 maybe since LMNA is associated with AD cardiomyopathy but MR22 has multiple additional features such as severe developmental delay.

3. Based on what's described the text, patient MR22 cannot be classified as 'molecularly diagnosed' with mutations in known genes

4. Authors should describe more in detail why genetic diagnosis of these patient cohorts is needed and why they think exome sequencing is a preferred method to other tests (i.e. gene panel) and also mention what are some drawbacks of doing exome sequencing instead of panels.

Minor concerns

1. "Next-generation exome sequencing" and "whole-exome sequencing" should be changed to "exome sequencing"

2. References needed for page 3 line 37

3. Was this study approved by the IRB? It should be mentioned in the patient selection paragraph

4. The methods for DNA extraction and exome sequencing are too lengthy. Both used commercially available kits so there is no need to describe in detail how the methods work unless there were modifications made.

5. In page 4 line 43-44, which exome/genome databases were used and which in silico prediction scores were used? Add exact name and references.

6. Page 5 first paragraph should either move to methods>data analysis paragraph or become a separate section under results

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.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
No

**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

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