

Review of: "Penetrance and disease expression of (likely) pathogenic variants associated with inherited cardiomyopathies in the general population"

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This manuscript has conducted exome data analysis of the 200,643 UK Biobank individuals. They have sorted the likely pathogenic and pathogenic variants in the ACM, DCM and HCM associated genes. A prevalence of pathogenic variants have been identified like the below:

ACM: 1:578; DCM: 1:251; HCM: 1: 149. Genotype positive individuals have increased mortality and morbidity, in particular for DCM and HCM variant carriers. This is not particularly true for ACM genotype positive carriers, though they have had significantly elevated risk of cardiac arrhythmia.

I consider the manuscript is a very nice manuscript. It is well written and data are informative and has been arranged nicely. I have only three minor (may be major) comments:

1. Khera AV et al. (J Am Coll Cardiol. 2019;74:2623–34) have conducted a similar study, where they have shown that 1% of the general population are carriers of a pathogenic variant in one of the cardiac disease causal genes. How would you correlate or compare your findings with Khera et al.
2. Lorenzini et al (J Am Coll Cardiol 2020;76:550–9) showed that a HCM pathogenic variant carriers overtime have 50% chance to develop HCM, which is significantly different from your study. How would you explain the difference ?
3. Escobar-Lopez et al (J Am Coll Cardiol 2021;78:1682–1699) showed that genotype positive people have more propensity to have cardiovascular events than genotype negative people. Further, they showed that TTN truncating mutation carriers exert less phenotype and they have got more chance for reverse remodelling. Do you have any such data from your study ? What about LMNA mutation carriers ?