Monogenic Basis of Hypertrophic Cardiomyopathy; What to Expect from the Commercially Available Genetic Tests ?

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BACKGROUND

We sought to define the status of genetic variation contributing to hypertrophic cardiomyopathy (HCM) and to compare inclusiveness and inter-panel variability of genetic testing panels for HCM available in the United States.

METHODS

Using ClinVar, Ensemble Project and gnomAD (v.2.1.1.) datasets to gather the total number, relative frequencies, and clinical consequence of variants reported to cause HCM phenotype.

The pathogenicity of each variant was determined based on the American College of Medical Genetics standards to generate a comprehensive variant list and draw the monogenetic architecture of HCM.

The pre-curated gene lists of four different commercially available genetic testing panels for HCM were extracted (Laboratory for Molecular Medicine, Invitae, GeneDx, and Baylor College of Medicine).

The total number and frequencies of pathogenic/likely pathogenic variants included in each commercially available HCM genetic testing panel were compared.

RESULTS

The ClinVar database contained 15,983 variants that were associated with HCM phenotype. Considering the relative frequencies, impact on protein structure, and clinical annotation, only 1120 (6.9%) variants in 107 genes were classified as pathogenic/likely pathogenic. Leading genes were MYBPC3 (16.6%), GAA (11.1%), ACADVL (8.7%), AGL (8.0%), and MYH7 (6.1%) accounting for 566 (50.4%) of disease-causing variations. Only 342 (30.5%) of pathogenic/likely pathogenic variants in 16 genes were consistently curated in all genetic testing panels. Remaining disease-causing variants were not consistently considered in genetic testing panels.

Figure 1. MYBPC3 mutations is the main etiology of HCM

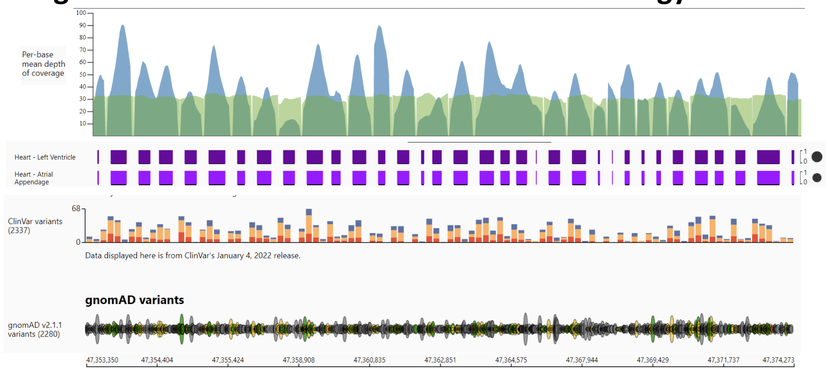


Figure 2. MYBPC3 is exclusively expressed in heart tissue Reduction in MyBP-C relative to myosin alters sliding velocities as actin-myosin sliding reaches the C-zones, where MyBP-C is specifically present, resulting in a more rapid contractile deceleration toward peak force development

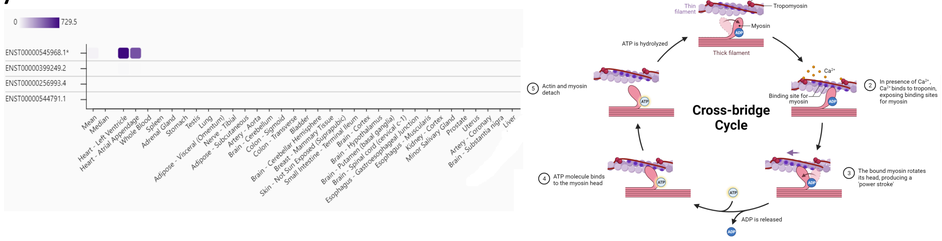
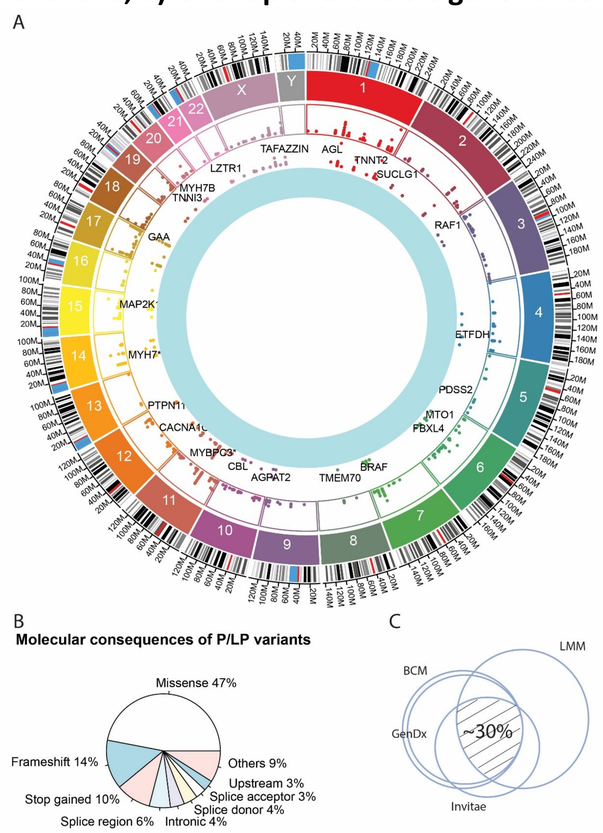


Figure 3. A) Circus plot of all P/LP variants underlying HCM, B) Types of mutations, C) Overlap of available genetic test panels



CONCLUSIONS

This study showed a comprehensive picture on genetic architecture of HCM as well as considerable variability in commercially available HCM genetic testing panels. Before genetic testing it is imperative to customize testing panel with respect to the individual's phenotype. With expansion of the current genotype-phenotype association knowledgebase, there is a need for continues revisiting and standardization of curation and reporting of the genetic test results for HCM.

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