Diagnostic yield and mutation spectrum of multigene panel testing for hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease with a worldwide prevalence of 1:500, and is the leading cause of sudden cardiac death in young people. Genetic etiology is suspected in up to 50% of HCM patients, and genetic testing is highly recommended for HCM patients and family members following the identification of a causative mutation in the proband. To gain insight into the diagnostic yield and mutation spectrum of HCM, a retrospective review was performed for 408 consecutive cases with a clinical suspicion of HCM who underwent multigene panel testing at our laboratory. A pathogenic mutation was identified in 27% (n=112) of these individuals. Eighty two pathogenic mutations in 15 genes were identified. The most frequently mutated genes were *MYBPC3* (48%)*, MYH7* (21%)*, TNNT2* (9%) and *MYL3* (5%). Further variant-specific analysis identified 38 individuals from 31 families who were positive for the mutation previously identified in their respective probands. The median age for mutation-positive individuals reported to have cardiomyopathy was 38 years (n=5) vs 14 years (n=21) for unaffected mutation-positive individuals, consistent with the age-related penetrance of HCM. This underscores the great utility of genetic testing in identifying pre-symptomatic at-risk individuals. In our study, the diagnostic yield is lower than the value reported in the literature, which may be explained by i) the presence of variable phenotypes in individuals who underwent testing on larger panels designed to detect multiple types of cardiomyopathy, ii) testing of unaffected individuals referred solely due to their family history, iii) differences in testing criteria for research studies compared to that for clinical testing, iv) the lack of clear phenotype information in some cases, or v) the strict variant interpretation guidelines used in a clinical diagnostic laboratory, which results in more frequent reporting of variants of uncertain significance (VUS). In the current cohort, VUS were detected in 46% of the individuals (n=189), including 34 probands who had pathogenic mutations. About one third of the VUS were in *TTN*, followed by *MYH6, MYH7,* and *MYBPC3*. VUS interpretation is challenging and will benefit from continually emerging data, including population frequency estimates in larger and more ethnically diverse populations, familial co-segregation studies, and functional studies.