All in the Family: How Family History Affects Diagnostic Yield of Hypertrophic Cardiomyopathy Multigene Panel Testing

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Family history is often a predictor of disease. For hypertrophic cardiomyopathy (HCM), a family history (fhx) is seen in approximately 72% of cases in which a mutation is identified (1). To further assess the relationship between fhx of HCM and the probability of identifying a pathogenic mutation in a HCM-associated gene, we examined the family history of all probands with HCM who underwent multigene panel (MGP) testing at our diagnostic laboratory from April 2015 to June 2016. Particular emphasis was placed on analysis of MYBPC3 and MYH7. Clinical history was collected from test requisitions, available pedigrees and clinical notes.

Among 237 patients referred for HCM MGP testing, 32% (n=77) were positive for a mutation, the majority of which were in MYBPC3 (n=44; 57%) and MYH7 (n=13; 17%). Among the 57 HCM probands with positive MGP testing results who reported fhx information to our laboratory, 84.2% (n=48) reported 'some cardiac fhx.' This included 36.8% (n=21) reporting a fhx of HCM, 28.0% (n=16) reporting a fhx of sudden cardiac arrest (SCA), In addition, 15.8% (n=9) reported no cardiac fhx. Probands with mutations in MYBPC3 had a higher frequency of reporting a fhx of HCM (14/34; 41.2%) or SCA (10/34; 29.4%), compared to probands with MYH7 mutations, in which fhx of HCM was reported in 22.2% (2/9) of probands and fhx of SCA was reported in 22.2% (2/9) of probands. Approximately half of the MYBPC3 mutations were either protein truncating, haploinsufficient or splice site mutations (52.2%), while the remainder (47.7%) were missense mutations, whereas MYH7 mutations were exclusively missense alterations, consistent with the mechanism of disease for this gene.

The prevalence of fhx of HCM and SCA in our cohort is lower than previously published rates of 72% and 89% (1), respectively. This may reflect ascertainment bias in previous cohorts, or an uptake of genetic testing among singleton cases of HCM in recent years. Nevertheless, these data demonstrate a role for genetic testing among sporadic or familial cases of HCM. Cardiologists and other healthcare providers should still take a thorough fhx among patients newly diagnosed with HCM. Further exploration of genotype-phenotype relationships will be valuable for better understanding the predictive value of genetic testing for HCM and may be useful in family risk counseling.

1). Genet Med. 2013 Dec;15(12):972-7. doi: 10.1038/gim.2013.44. Epub 2013 Apr 18.

2). Circ Cardiovasc Genet. 2013 Feb; 6(1): 118–131.