LEVERAGING SIGNAL-TO-NOISE ANALYSIS TO EXPAND CLINICAL UTILITY OF PATHOGENICITY CRITERIA FOR INCIDENTAL VARIANTS IN HYPERTROPHIC CARDIOMYOPATHY-ASSOCIATED GENES

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Background: Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy and can predispose individuals to sudden death. Most HCM patients host a known pathogenic variant in a sarcomeric gene. With the increase in exome sequencing (ES) in clinical settings, known pathogenic variants in HCM-associated genes are being identified more frequently. Diagnostic interpretation of incidental variants is crucial to enhance clinical patient management.

Objective: We sought to use amino acid-level signal-to-noise (S:N) analysis to establish pathogenic hotspots in sarcomeric HCM-associated genes as well as to refine the 2015 American College of Medical Genetics (ACMG) criteria to predict incidental variant pathogenicity.

Methods: Incidental variants in HCM genes (MYBPC3, MYH7, MYL2, MYL3, ACTC1, TPM1, TNNT2, TNNI3, TNNC1) were obtained from a clinical ES referral database (Baylor Genetics) and compared to rare population variants (gnomAD) and variants from HCM literature cohort studies. We compared the frequency of ES and HCM variants at specific amino acid locations in coding regions to rare variants (MAF < 0.0001) in gnomAD. S:N ratios were calculated at the gene- and amino acid-level to identify pathogenic hotspots. ES cohort variants were re-classified using ACMG criteria with S:N analysis as a correlate for PM1 criteria.

Results: We identified 7,066 unrelated probands in the ES cohort, with 509 individuals hosting a rare variant in an HCM gene. Variants in sarcomeric genes, especially radical variants, were enriched in the HCM cohort compared to ES and gnomAD cohorts (p < 0.05). In the HCM cohort, five out of nine genes carried a S:N ratio greater than 6.0, suggesting a higher relative frequency of disease-associated variants in these genes. Among ES referrals, no gene had a global S:N greater than 3.0. Within each gene, localization of variants found in the ES cohort was more similar to those found in gnomAD than those found in the HCM cohort. In MYH7, most pathogenic hotspots were in the head domain.

Conclusion: Incidental variants in HCM-associated genes were common among clinical ES referrals, though the majority were not disease-associated. Leveraging amino acid-level S:N as a clinical tool may improve the diagnostic discriminatory ability of ACMG criteria by identifying pathogenic hotspots.