Examining Prevailing Genotype-Phenotype Correlations in Hypertrophic Cardiomyopathy: Findings From the Sarcomeric Human Cardiomyopathy Registry (SHaRe)

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Introduction:
The Sarcomeric Human Cardiomyopathy Registry (SHaRe) was established to amass robust large-scale, longitudinal genotype, phenotype, and outcomes data for HCM. Here we examine prevailing concepts regarding genotype and phenotype in HCM.

Methods:
Seven HCM centers in the United States, Europe, and Brazil mapped key fields from existing databases to a central database. Genetic testing interpretation was standardized. Two-sample t-test or Fisher's exact test assessed differences among genotypic subgroups. Composite (EF<55%, ICD shock, Afib, stroke, septal reduction, heart failure, cardiac arrest, death), heart failure, and arrhythmic cardiovascular events were assessed with Kaplan-Meier log-rank tests.

Results:
Of 4686 HCM patients, 2184 unrelated probands (54%) underwent genetic testing. Of these, 963 probands had pathogenic or likely pathogenic mutations (sarcomere(+)) and 1014 had no mutations (sarcomere(-)). Compared to sarcomere(-), sarcomere(+) probands were 12.4 yrs younger at diagnosis and had earlier development of AFib and composite outcome, as well as heart failure, and arrhythmic outcomes (p<0.001 for all; Figure). Probands with MYH7 mutations were 2.2 yrs younger at diagnosis and had earlier development of AFib and composite outcome than other sarcomere(+) probands. Probands with ≥2 mutations were 6.2 yrs younger at diagnosis reached composite and arrhythmic outcomes earlier than other sarcomere(+). LV wall thickness and outcomes were not significantly different in thin vs thick filament probands.

Conclusions:
This is the largest clinical study of genotyped HCM patients. Probands with sarcomere mutations, MYH7, and ≥2 mutations have more severe clinical profiles. Continued expansion of this cohort and novel approaches to genotype-phenotype analysis are required to gain further granularity, new insights into the biology of HCM, and to identify better predictors of prognosis.
Figure Composite outcomes for hypertrophic cardiomyopathy patients (LVEF <55%, appropriate ICD firing, atrial fibrillation, stroke, septal reduction therapy, transplant/LVAD, NYHA III or IV, resuscitated cardiac arrest, or death from any cause) based on genotypic subgroups (patients with n=1,095) vs. without (n=973) pathogenic or likely pathogenic sarcomere mutations, patients with thick-filament (n=985) vs. thin-filament (n=110) mutations, patients with mutations in MYH7 (n=355) vs. MYBPC3 (n=598), patients with 1 sarcomere mutation (n=1,053) vs. >1 (n=42) sarcomere mutation.

Disclosure:
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