RISK STRATIFICATION IN CARDIOMYOPATHIES: WHAT’S NEW AND CLINICALLY RELEVANT?

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High-throughput genotyping and phenotyping reveals new genetic determinants of clinical phenotype in hypertrophic cardiomyopathy
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Background: A major barrier for the clinical application of genetics in hypertrophic cardiomyopathy (HCM) is a lack of data on the relation between genotype and phenotype.

Aim: Discover new genetic determinants of HCM phenotype using high-throughput genotyping.

Methods: Unrelated and consecutive patients (pts) were studied. High-throughput sequencing was used to analyze 41 genes. Rare variants (vts) were tested for associations with the phenotype.

Results: The cohort comprised 384 pts (46.5±15.1 years at initial evaluation, 71.4% males). Candidate sarcomere or sarcomere-associated vts were present in 240 pts (63%). Seventy-five percent were either previously published or novel loss-of-function or insilico predicted to be pathogenic. Rare vts in desmosomal and ion-channel genes were each present in 88 (23%) pts. Table 1 shows some of the significant genotype-phenotype associations.

Conclusions: Genotype-phenotype relationships, some of them novel, were identified for sarcomeric and related genes. Non-sarcomeric vts seem to have a phenotype-modifier effect.

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Outcome of hypertrophic cardiomyopathy associated with sarcomere protein gene mutations: impact of the implantable cardioverter-defibrillator
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Objectives: The purpose of this study was to investigate the impact of the implantable cardioverter-defibrillator (ICD) on patients with hypertrophic cardiomyopathy (HCM) and sarcomere gene mutations.

Methods: Of 269 pts (M/F 166/103, age range 18 to 88 years, mean age 53.8±15 years) who met the inclusion criteria, 89 pts were included in this study. All pts underwent an initial evaluation and were followed-up for a mean duration of 2.8±1.9 years. The endpoint was all-cause mortality or cardiac death (CD).

Results: At initial evaluation, 63.4% of pts had a left ventricular ejection fraction (LVEF) ≤ 50%, 52% had moderate-severe diastolic dysfunction, and 55.8% had a history of syncope. Among the pts, 10% had a family history of sudden cardiac death (FHS). The risk of death was significantly higher in pts with a history of syncope (OR 2.49, CI 1.04, 5.91), a positive exercise test (OR 2.46, CI 1.04, 5.79), and LVEF < 40% (OR 2.32, CI 1.18, 4.55). The presence of late enhancement (LE) in MRI was rare in the pts of the registry. There was no significant significant correlation between the presence of LE and events. The analysed risk factors showed no correlations to events in the registry. The survival at 5 years was 84% for pts with and 90% for pts without LE in MRI (log-rank test, p=0.003).

Conclusions: The results of this study suggest that pts with HCM and sarcomere gene mutations have a high risk of death, especially due to cardiac death. Therefore, it is important to consider the use of ICD therapy in these pts. Further studies are needed to validate these findings and to explore the potential benefits of ICD therapy in pts with HCM and sarcomere gene mutations.