ACC.15
TCT@ACC-i2 | innovation in intervention

A958
JACC March 17, 2015
Volume 65, Issue 10S

Heart Failure and Cardiomyopathies

THE R21C MUTATION IN TROPONIN I HAS A FOUNDER EFFECT IN SOUTH LEBANON AND CAUSES MALIGNANT HYPERTROPHIC CARDIOMYOPATHY

Poster Contributions
Poster Hall B1
Sunday, March 15, 2015, 3:45 p.m.-4:30 p.m.

Session Title: Genetic Interactions in Heart Failure
Abstract Category: 13. Heart Failure and Cardiomyopathies: Basic
Presentation Number: 1215-180

Authors: *Akl Fahed, Georges Nemer, Fadi F. Bitar, Samir Arnaout, Antoine B. Abchee, James Ware, Manal Batrawi, Steven R. DePalma, Barbara McDonough, Mariam T. Arabi, Jonathan Seidman, Christine Seidman, Harvard Medical School, Boston, MA, USA*

Background: Although gene testing is widely available for Hypertrophic Cardiomyopathy (HCM), determining the clinical implications of a mutation is limited by an understanding of its phenotype. Inbred populations with founder mutations provide an opportunity to study genotype-phenotype correlations.

Methods: We recruited 28 Lebanese families with HCM. Index patients from 20 families received targeted sequencing for a panel of sarcomere protein genes including TNNI, and 7 families received Sanger sequencing for the TNNI gene.

Results: We identified a missense mutation R21C in the TNNI gene segregating with HCM in four families from South Lebanon (14.3% of the total Lebanese cohort and 67% of the South Lebanon cohort). Also 504 control subjects from Lebanon tested negative for the R21C mutation (OR>84, p-value<0.0001). Through cascade screening, we identified 30 patients from the four families that are heterozygous for the TNNI R21C mutation. Twenty (67%) of them had a clinical diagnosis of HCM with a median age of 37 years, while 9 (30%), with median age 21 years, had no evidence of HCM on echocardiography. An additional 27 members of the families had evidence of HCM, including 22 with SCD in the setting of no past medical history, and their carrier status for R21C was implied from the pedigrees. Survival analysis for 57 HCM patients with the mutation revealed a markedly decreased age at first adverse event as compared to 47 HCM patients with the MYBPC3 R502W mutation. Additional phenotyping of selected members showed cardiomyocyte disarray on autopsy heart of patient who had SCD in the absence of hypertrophy, as well as suggestive findings on myocardial tissue Doppler and cardiac MRI in genotype positive patients with a normal echo.

Conclusion: Founder mutations in HCM that cause a severe phenotype are uncommon. The R21C mutation in TNNI is the first HCM mutation described in the Lebanese population and has a founder effect in South Lebanon. The R21C mutation in TNNI is associated with severe cardiac hypertrophy and/or sudden deaths at a young age. Early and more frequent screening with different imaging modalities as well as tailored management might be warranted for carriers of this mutation.