FHL2 expression and variants in hypertrophic cardiomyopathy.

Abstract:
Based on evidence that FHL2 (four and a half LIM domains protein 2) negatively regulates cardiac hypertrophy we tested whether FHL2 altered expression or variants could be associated with hypertrophic cardiomyopathy (HCM). HCM is a myocardial disease characterized by left ventricular hypertrophy, diastolic dysfunction and increased interstitial fibrosis and is mainly caused by mutations in genes coding for sarcomeric proteins. FHL2 mRNA level, FHL2 protein level and I-band-binding density were lower in HCM patients than control individuals. Screening of 121 HCM patients without mutations in established disease genes identified 2 novel (T171M, V187L) and 4 known (R177Q, N226N, D268D, P273P) FHL2 variants in unrelated HCM families. We assessed the structural and functional consequences of the nonsynonymous substitutions after adeno-associated viral-mediated gene transfer in cardiac myocytes and in 3D-engineered heart tissue (EHT). Overexpression of FHL2 wild type or nonsynonymous substitutions in cardiac myocytes markedly down-regulated ?-skeletal actin and partially blunted hypertrophy induced by phenylephrine or endothelin-1.
After gene transfer in EHTs, force and velocity of both contraction and relaxation were higher with T171M and V187L FHL2 variants than wild type under basal conditions. Finally, chronic phenylephrine stimulation depressed EHT function in all groups, but to a lower extent in T171M-transduced EHTs. These data suggest that (1) FHL2 is down-regulated in HCM, (2) both FHL2 wild type and variants partially protected phenylephrine- or endothelin-1-induced hypertrophy in cardiac myocytes, and (3) FHL2 T171M and V187L nonsynonymous variants induced altered EHT contractility. These findings provide evidence that the 2 novel FHL2 variants could increase cardiac function in HCM.