NUCLEAR RECEPTOR CO-ACTIVATOR-1 MODIFIES THE HYPERTROPHIC CARDIOMYOPATHY PHENOTYPE

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Background: Variability in hypertrophic cardiomyopathy (HCM) phenotypic expression is not fully explained by underlying sarcomeric gene mutations and a role for genetic modifiers is supported by animal and human studies. Extreme ventricular hypertrophy is a phenotype associated with sudden cardiac death. Because variants in the estrogen pathway are known to be associated with left ventricular mass in the general population, we hypothesized that estrogen pathway variants are associated with wall thickness in HCM.

Methods: We examined the association between echocardiographically assessed maximum left ventricular wall thickness (MLVWT) and 190 single nucleotide polymorphisms (SNPs) within 28 candidate genes in a screening cohort of 110 patients with HCM. We confirmed the results of our screening study in an additional 61 subjects.

Results: 167 patients had complete phenotype and genotype data (57% male; mean age 45.9 ± 15.6 years; mean MLVWT 19.7 ± 6.0 mm, range 11 to 51 mm). Multivariate models adjusting for age and gender revealed no association between estrogen receptor SNPs and MLVWT. In contrast, a SNP in the nuclear receptor coactivator-1 (NCOA1) gene (rs13034651) was significantly associated with MLVWT (unadjusted p ≤ 0.0001, Bonferroni adjusted p = 0.034). No other echocardiographic or clinical variables in our screening cohort were significantly associated with rs13034651. There was a significant difference between mean MLVWT of the major homozygous, heterozygous, and minor genotypes in a general model adjusted for age and gender (N=167: AA 23.4 ± 8.8 mm; AT 18.7± 4.8, TT 18.6 ±4.0 mm, p ≤0.0001).

Conclusions: Our data suggest that the NCOA1 gene modifies the HCM phenotype. Rapid ventricular growth in HCM typically occurs during the pubertal growth spurt. By coding for a receptor co-activator protein that modifies thyroid hormone-, androgen-, glucocorticoid-, and estrogen-receptor-dependent transcription, the NCOA-1 gene may affect the severity of hypertrophy in HCM via regulation of sex and nuclear hormone receptor signaling, possibly during adolescence.