Evaluation of PGC1alpha Gene Variants in Modulating Hypertensive Heart Disease Phenotypes

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Abstract

Peroxisome proliferator-activated receptor-γ coactivator-1 α (PGC1α), a co-activator for nuclear receptors, regulates mitochondrial biogenesis and fatty acid β-oxidation. Altered expression of PGC1α has been associated with left ventricular hypertrophy and dilated cardiomyopathy. **Hypothesis:** Single nucleotide polymorphisms (SNPs) of PGC1α are associated with hypertensive heart disease phenotypes such as abnormal diastolic function, systolic function, and/or increased left ventricular mass (LVM). **Methods:** Thirty-nine SNPs were genotyped in 395 Caucasians (age 50±13, female 54%) and 134 African Americans (age 49±12, female 69%). Diastolic function was assessed by tissue Doppler imaging-derived early diastolic mitral annular velocities (Em) of the lateral (Em_lateral) and septal (Em_septal) portions of the mitral annulus, where lower values represent impaired diastolic function. LVM was measured by M-mode and indexed by height^{2.7} (LVM/Ht^{2.7}). Left ventricular ejection fraction (LVEF) was calculated by the method of discs. The presence and strength of association of PGC1α SNPs with hypertensive heart disease phenotypes were evaluated by regression analyses of age- and sex-adjusted trait values. The relative importance of individual PGC1α variants was assessed by multiple-SNP analysis, and confounding effects were controlled by including known covariate of hypertensive heart diseases in stepwise regression models. **Results:** Most SNPs were in Hardy-Weinberg equilibrium in both races with concordant minor alleles. Linear regression found significant associations of LVM/Ht^{2.7} and indices of diastolic function with several SNPs. One SNP associated with Em_lateral in both races was rs2970869 (Caucasian, minor allele frequency [MAF]=23%; G/G[n=254] 12.9±0.16 vs. A/G[n=125] 13.6±0.23 vs. A/A[n=14] 13.6±0.68 cm/sec, p=0.04; African American, MAF=8%; G/G[n=92] 12.2±0.24 vs. A/G[n=36] 13.1±0.39 vs. A/A[n=6] 14.8±0.93 cm/sec, p=0.007). Stepwise regression with covariates typically found more significant associations than did single-SNP analyses. The rs2970869 SNP remains significantly associated with Em_lateral in both race groups in multiple-SNP analyses where covariates and other associated SNPs were included in the model. Associations of other SNPs with indices of diastolic function and LVM/Ht^{2.7} were not shared by the two racial groups. No associations were found with systolic function. **Conclusion:** The PGC1α promoter variant rs2970869 resides in a putative TFIID binding site consensus sequence and may play a role in modulating diastolic function. The higher A-allele frequency in Caucasians is consistent with the lower prevalence of diastolic dysfunction, and may help explain their lower morbidity and mortality compared to African Americans with hypertension. Overall, these findings suggest that PGC1α may have a role in modulating the hypertensive heart disease phenotype.