Dissecting the Role of CD36 in Metabolic Genetic Pathways to Hypertensive Heart Disease

Lisa de las Fuentes, MD

Mentors: C. Charles Gu, PhD
Víctor G. Dávila-Román, MD

Abstract

Hypertensive heart disease (HHD) resulting from long-standing hypertension, manifests early as left ventricular hypertrophy (LVH) and/or left ventricular diastolic dysfunction (LVDD). Although initially an adaptive response, over time LVH and LVDD become maladaptive leading to left ventricular (LV) enlargement, systolic dysfunction, and/or heart failure (HF). The molecular and/or genetic mechanisms responsible for the development of LVH and/or HHD have not been well characterized; however, alterations in myocardial substrate metabolism are important determinants of the presence and development of LVH in animal models of pressure-overload and in humans with LVH and HF. Long-chain fatty acids enter the heart via the protein-facilitated transporter, CD36, which has promoter elements shown to confer tissue-specific expression entrained to substrate availability. We hypothesize that CD36 gene variations modulate HHD phenotypes in humans and interact with other key metabolic regulatory genes.

Cardiovascular (CV) phenotypes were characterized by physical examination, serum chemistries, echocardiography, and carotid artery ultrasonography. In addition to measured HHD-traits (i.e., ultrasound indices of LV structure/function and carotid artery intima media thickness), latent HHD traits were extracted by independent component analysis. Haploview Tagger (v. 3.32) was used to identify LD-based race-specific tagSNP sets ($r^2$ threshold >0.8) using CEU and YRI HapMap genotypes, supplemented by additional SNPs with reported biologic function. CD36 SNPs were genotyped using Sequenom MassArray technology. Agreement with Hardy-Weinberg equilibrium was tested using the chi-square goodness-of-fit test. The presence and strength of association between CD36 gene variants and HHD traits were tested within a case-control sample within race groups. Linear multivariable regression analyses tested for marginal effects between the dependent variables and individual CD36 variants. Association analysis of interaction effects were carried out by first examining within-gene interactions using regression analyses against haplotypes in identified LD blocks in CD36, and then followed by exploratory analysis of gene-gene interactions between CD36 and PPARα, PPARγ, and PGC1α in a subpopulation using Bayesian network (BNT) analyses.

The study cohorts consisted of Caucasian (C, n=608) and African-American (AA, n=228) adults representing a wide-variety of CV and/or metabolic diseases, as well as normal controls. In C and AA, 14 and 52 CD36 SNPs, respectively, passed a quality assurance evaluation. No significant marginal effects for individual CD36 SNPs were detected by multivariable regression models in C; however, 3 CD36 haplotypes were associated with LV diastolic function, LV mass, and LV ejection fraction suggesting a role for interaction of cis-acting elements. In AA, significant associations were noted between 15 individual SNPs and 17 CD36 haplotypes with indices of LV diastolic function, LV mass, and latent HHD traits. Exploratory BNT analyses including significant SNPs and estimated haplotypes in the four genes identified meaningful cis- and trans-acting gene-gene interactions in both races, with substantive evidence that obesity (BMI) plays an important modulating role. Both marginal effects and gene-gene interactions are noted between CD36 gene variants and HHD-related traits. While marginal effects were notably small in the Caucasian sample, within gene interaction among variants from the 2 regions of CD36 seems to have an important role in modulating the HHD traits. Exploratory BNT analyses highlight the complex nature of interactions among CD36 and metabolic regulatory genes, a finding that deserves further investigation given the importance of this candidate pathway in determining CV phenotypes.