Association and Interaction of PPAR-complex Gene Variants with Latent Traits of Left Ventricular Diastolic Dysfunction

Jyh Ming (Jimmy) Juang, MD., M.S.

Mentors: Victor Dávila-Román, M.D.
        C. Charles Gu, Ph.D.
        Lisa de las Fuentes, M.D., M.S.

Abstract

Left ventricular diastolic dysfunction (LVDD) includes abnormalities of LV filling and relaxation, an energy-dependent process. Myocardial fatty acid metabolism has been associated with indices of LV diastolic function in animal models and in humans. However, it is unclear whether (or how) variants in genes that regulate myocardial energy metabolism play a modulating role in this process. Recent work has demonstrated the potential for improved understanding of genotype-phenotype associations for hypertensive heart disease (HHD, of which LVDD is a special case) by using latent traits derived from multivariate endophenotypes of HHD. In the present project, we apply the same approach of latent trait analysis to a selective subset of LVDD-related endophenotypes and explore in detail their associations with 64 single nucleotide polymorphisms (SNPs) in 3 PPAR-complex genes involved in the transcriptional regulation of fatty acid metabolism. In addition, a novel statistical learning method of ridge regression is used to select and account for significant interaction effects from a large number of possible within-gene and cross-gene interactions. The latent LVDD traits were extracted from a panel of 11 multi-dimensional “raw” echocardiographic measures of LV relaxation and filling using independent component analysis (ICA). The single-SNP associations with the derived latent LVDD trait were tested by regression analysis in 403 Caucasians (46% male, age: 50 ± 12 yrs, body mass index: 30 ± 6 kg/m2, hypertension 37%). Potential confounding of known covariates including age, sex, and LV mass were properly adjusted by step-wise regression. We found 9 SNPs (6 in PPARα and 3 in PGC1α) significantly associated with the latent LVDD trait, whereas only 1 SNP was associated with measured “raw” echocardiographic indices. The problem of very large number of predictor variables (SNPs) and their interactions in the general regression model and of potential collinearity among some of the SNPs were addressed by ridge regression for effective variable selection. As an exploratory analysis, all SNPs within each gene (i.e. gene-centric analysis) were included in the ridge regression analysis. Those SNPs with either marginal effects or within-gene interactions selected by the initial ridge regression were entered into a second ridge regression to select the final model that accounts for cross-gene interactions. In the final model, 15 individual SNPs (5 PPARα, 3 PPARr and 7 PGC1α) were retained as significant. In addition, the model retained 19 pairwise SNP-SNP interactions (log likelihood -85.3). Two significant interactions were within-gene, probably reflect cis-interacting elements; three significant interactions were between-gene, highlighting the potential for interdependency of these gene products by affecting transcription factor binding motifs that regulate the expression of metabolism genes.

In conclusion, the latent trait analysis worked well in teasing out the important genotype-phenotype associations for LVDD and variants in metabolism genes; and the results strongly support that the myocardial metabolism genes may play an important role in modulating LV diastolic function in HHD.