Latent Factors in High-dimensional Hypertensive Heart Disease Related Phenotypes

Hugh Flores

Mentors:
Dr. C. Charles Gu
Dr. Victor Dávila-Román

Abstract

Hypertensive heart diseases (HHD) are the most common subset of cardiovascular disease and encompass a host of inter-related conditions that include hypertension, left ventricular hypertrophy (LVH), left ventricular systolic dysfunction, and left ventricular diastolic dysfunction. These primary phenotypes commonly occur in the setting of other co-morbid conditions, including diabetes, obesity, metabolic syndrome, and vascular hypertrophy. The co-morbid relationship between these diseases has led some to speculate that they may have a common underlying pathologic process. Because of the complexity of the primary traits, recent studies turned to examining a host of intermediate phenotypes, such as echocardiographic measures, for more useful insight. However, the use of many intermediate traits introduces the problem of high-dimensionality in the phenotypic domain. A dimension-reduction strategy is needed to identify fewer intrinsic patterns in the high-dimensional data that may be used as latent traits to reflect more closely the underlying pathophysiology of the disease resulting in groupings of subjects more homogeneous both in phenotypic and in genotypic domain and will potentially lead to more powerful genetic study of the disease traits. To accomplish this goal, we introduce a new statistical method called Independent Component Analysis (ICA) and apply the methodology to extract latent traits of HHD from high-dimensional echocardiographic and metabolic data collected in a prospective study of the metabolic predictors of LVH currently being conducted at Washington University. The ICA-extracted latent trait of HHD seemed to summarize well the various intermediate phenotypes and exhibit a high concordance with the set of primary clinical indicators of HHD. More interestingly, genetic association analysis of the latent trait with several SNPs in candidate genes of HHD resulted in several significant findings, while the same analysis done on the original clinical phenotypes of HHD did not. One of the SNPs found in association with HHD, the Intron 7 G>C (rs4253778) has been previously shown to be associated with LV mass and lipid response to drug therapy. The other PPARα SNP (L162V) has been shown to affect plasma lipid levels independently and in interaction with diet and be associated with components of the MS. It was interesting that in our analysis, the Intron 7 G>C SNP was identified as significant in both races by both univariate and multivariate analysis. However, the exon SNP L162V in the same gene was picked up in whites, but not in blacks. While the smaller sample size of blacks could be responsible, the observation led us to speculate there is genetic heterogeneity.