Linkage Analysis of Metabolic Syndrome and Echocardiographic Phenotypes in the HyperGEN Study

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Abstract

Metabolic Syndrome (MetS) and its risk factors are well-known predictors of future cardiovascular events. MetS is also directly associated with morphological and functional changes in the cardiovascular system. Therefore, we hypothesized that the individual risk factors of MetS may be highly correlated with left ventricular (LV) features of the heart because of shared genetic effects (pleiotropy). By accounting for correlations among risk factors, genomic regions that co-regulate these traits may be identified.

Multivariate Factor Analysis (FA) was applied to eight MetS-related phenotypes and nine cardiac phenotypes under investigation, both with and without Varimax rotation. A smaller set of factors derived from FA were subsequently used in linkage analyses in search for QTLs. The latent structures and the QTLs found are reported for two cohorts of African Americans and Caucasians, also stratified by gender and diabetic status.

FA results suggested four to five factors: “LV Wall Thickness”, “LV Geometry”, “Obesity-INS”, “Lipid-INS”, and “BP” factors. Four factors were sufficient when Varimax rotation was not applied. However, all five were necessary when the rotation was applied.

Linkage results identified three candidate regions with LOD scores over 3 in the African American population, “Obesity-INS” factor at 2p21 (LOD = 3.94) and 12q21.33 (LOD = 3.27), and “BP” factor at 19q13.31 (LOD = 3.04). In Caucasian samples, QTLs were found for “LV Wall Thickness” at 3p12.1 (LOD = 2.43) and 16q23.3 (LOD = 2.57). Region 16q23.3 contains a heart cadherin gene, Cadherin 13 (CDH13). Factors involving both MetS and ECHO variables only had suggestive linkage evidence for “BP-LV Dimension-Wall Thickness” at 3q29 (LOD = 2.56) and 20p13 (LOD = 2.44) and probable peak for “BP-LV Geometry” at 3q27.3 (LOD = 1.78) in Caucasians.

The findings represent a new epidemiologic contribution, because to the best of our knowledge it is the first time where MetS risk factors and Echocardiographic phenotypes were simultaneously investigated.