An Investigation of Candidate Genes for Metabolic Syndrome through Protein-Protein Interactions: The HyperGEN Study

Rezart Kume

Mentors:  Aldi T. Kraja, D.Sc., Ph.D.
          Michael A. Province, Ph.D.
          D.C. Rao, Ph.D.

Abstract

Introduction: This aim of the current study is to expand the currently known hypothetical Network of 123 genes for metabolic syndrome (MetS), by identifying new genes that contribute to MetS pathways based on large protein-protein interaction (PPI) databases. Candidate genes identified this way are validated by association analysis of the MetS factors in the HyperGEN.

Methods: PPI genes were obtained from the NCBI databases and transformed into SAS datasets. All the PPI were merged with the 123 MetS genes list to find new interactant genes. The interactant genes were merged with dbSNP to find all possible single nucleotide polymorphisms (SNPs). Parallel with this work, family based association tests using linear mixed effects (LME) models on two samples of African Americans (n=908) and Caucasians (n=1,025) from the HyperGEN study were performed on the SNPs of interactant genes. Principal components (PC) analysis was performed on tagSNPs of African American sample via Eigenstrat to correct for any genetic admixture. We used the first 10 PC as covariates in the association analyses. The SNPs from interactant genes were matched with the SNPs found to be significant at (p<0.05). Only one SNP (the most significant one) was selected as the representative of a gene for each cohort sample.

Results: In African Americans’ LME analysis, only two PCs were found to be significant (p=0.02). After keeping only the most significant SNPs per gene, 425 and 375 genes, were identified respectively for African Americans and Caucasians. After Bonferroni corrections, 5 significant genes for African Americans were identified. Of them GNA14, (p<5.40E-5) associated with the Blood Pressure (BP) factor and CRADD, p<5.95E-6; SCARB1, p<9.77E-5 genes with Obesity Insulin (OI) factor. In Caucasians, 11 genes were considered significant. The most significant ones were associated with the BP factor (RANBP9, p<1.63E-5; FCGR2A, p<1.74E-5; HNF1B, p<2.19E-5) and with OI factor (NCAM2, p<2.09E-5).

Conclusion: Several new MetS genes were identified through PPI. Some of them were found to be significantly associated with MetS factors. Most of these new genes are supported by the literature. Use of PPI information proved to be a useful method to gain new insights about MetS.