

Genetic Association Analysis of Secondary Traits of Hypertension and a Functional Candidate Gene in the HyperGEN Study

Shamika Ketkar

Mentor: C. Charles Gu, Ph.D.

Abstract

Hypertension is a veritable global public health problem, affecting approximately 600 million people worldwide. Pathophysiology of hypertension involves interplay of many traits such as obesity, renal, metabolic and cardiovascular diseases. The application of genetic approaches to hypertension has aided in the delineation of molecular pathways underlying human blood pressure variation, in defining disease pathogenesis and identifying targets for therapeutic intervention. Many candidate genes have been linked to regulation of blood pressure, and polymorphic variants within such candidate loci are found associated with the diseases. Here we focus on the human angiotensinogen (AGT) gene, which was the first gene genetically linked to hypertension in humans. Several studies conducted over the past years, either to corroborate or to refute these claims, yielded highly inconsistent results. To better understand the role of AGT we executed series of conventional analyses to study the association of the AGT gene and secondary clinical and physiological traits of hypertension, namely, BMI, blood pressure responses to mental and physical challenges, and creatinine clearance, using 10 AGT SNPs genotyped in a sample selected from the participants of HyperGEN study. Additional analyses were performed to enhance our chances to identify real disease variants and to reduce false findings. Data on relatives from the same families (utilizing year-4 offspring) were used for applying family-based association methods (univariate and bivariate FBAT); and “functional information” of the SNPs was extracted via a comparative genomics approach from Promolign and public databases, and was incorporated into an extended ANOVA model. We detected highly significant associations between various AGT variants and blood pressure response to physical and mental challenges. Strong evidences of interaction among factors influencing the BP responses and renal function were observed with the bivariate FBAT analysis at the “well studied” promoter and exon2 SNPs (rs5051, rs699). Our association analysis benefited from utilizing functional information of the SNPs, and bivariate modeling as enhanced statistical significance was observed.