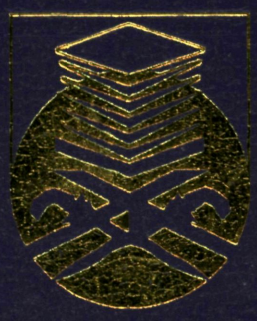

Genotype- Phenotype correlations in human cardiovascular diseases: Focus on hypertension and diabetes

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Abstract

Background and significance: Cardiovascular disease (CVD) is a multifactorial disorder resulting from both genetic and environment factors. Although there are many known environmental factors that contribute to CVD, the genetic underpinnings of CVD is less understood; and this is likely due to the complex relationship. With improvements in genetic technology, analysing the genetic underpinnings of CVD has become faster and less expensive. In this project, we evaluated the relationship between genetic variants of the endothelin receptor type A (EDNRA) gene and transcription factor 7-like 2 (TCF7L2) gene with hypertension and diabetes; two pathophysiological states that are highly associated with CVD. These genes may serve as markers for CVD.

Methods: Using a candidate gene approach, we evaluated the relationship between genetic variants and distinct CVD phenotypes using the HyperPATH cohort, a cohort consisting mostly of Caucasian individuals with mild hypertension, with or without diabetes. 683 and 344 individuals were studied for EDNRA and TCF7L2 project respectively. They completed two controlled dietary phases: high salt and low salt diet. Salt sensitivity of blood pressure, serum aldosterone, plasma renin activity, serum Potassium, homeostasis model assessment (HOMA-IR and HOMA-β), and renal blood flow on both high and low salt diet were determined in each subject. Statistical analyses were performed using general linear model accounting for appropriate covariates.

Results: SNP rs5335 of the EDNRA gene showed association with salt sensitivity in Caucasians from HyperPATH. Individuals with homozygous GG alleles are more likely to be salt sensitive with heightened serum aldosterone levels compared to the C carriers. In TCF7L2 analysis, we found association between SNP rs4081699 and rs7908486 and increased risk for diabetes. SNP rs7908486 were also found to be significantly associated with insulin sensitivity (HOMA-IR) and insulin secretion (HOMA-β) while SNP rs3814573 of TCF7L2 was found to be associated with insulin sensitivity (HOMA-IR) and baseline serum aldosterone (on low salt diet). However, all of the positive associations in TCF7L2 study were no longer seen after adjusting for age, gender, BMI and disease status.

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Introduction

Approximately 82 million American adults have 1 or more types of cardiovascular diseases (CVD) (Roger et al., 2012). According to National Center for Health Statistics, if all forms of major CVD diseases were eliminated, life expectancy could rise by almost 7 years. Almost $110 billion dollars was spend on healthcare and lost productivity of individuals with CVD (Heidenreich et al., 2011), highlighting the incredible burden these diseases place on healthcare system in the United States.

CVD are multifactorial disorders with complex pathophysiology. Many factors influence the development of CVD with both genetic and environmental underpinnings. Two well-known inheritable disease states, diabetes mellitus (DM) and hypertension, are strong predictors of CVD development (Sowers et al., 2001). An improved understanding of the relationship between various genetic variants and DM or hypertension would enable the development of improved strategies for successful diagnosis, therapy and prevention of CVD in humans. Thus, the goal of this project was to evaluate whether genetic variants associate with two cardiovascular related disease states; diabetes mellitus and hypertension in humans. Exploratory analyses were also conducted to evaluate whether a) the genetic variants were associated with measurements of vascular dysfunction and altered insulin secretion/utilization in humans and b) whether the environmental influence of sodium intake mediated any of the genotype-phenotype interactions.

CVD and Genetics

Currently, genotype phenotype relationships of complex disease pathophysiology such as CVD are difficult to examine (Herrmann and Paul, 2002).) The most widely tested markers in gene association studies are single nucleotide polymorphisms (SNPs (Lewis and Knight, 2012). SNP is a DNA sequence variation occurring when a single nucleotide in the genome is altered. Most SNPs have no effect on human's health. However, when a SNP is located in a coding or regulatory region near a gene, this may affect the gene's function. Some SNPs can predict an individual susceptibility to develop certain disease. A higher frequency of particular SNP variants among the diseased population can be interpreted as meaning that the particular variants increase the risk of a specific disease(Lewis and Knight, 2012). This