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COMMENTARY

Genetic association studies: hypertension and beyond

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Hypertension is one of the most prevalent cardiovascular conditions worldwide. Epidemiological studies have shown that blood pressure and electrolyte excretion vary across different races and ethnicities.[1] Understanding the molecular basis for these differences will provide useful insights into the prevention and treatment of hypertension and other related diseases. In this issue of Hypertension Research,[2] Liu *et al.* investigated the association between the α-adducin Gly460Trp polymorphism and essential hypertension risk by using meta-analysis. The results show that the Trp allele increases hypertension risk in a Han Chinese population, but not in a Kazakh population. This finding confirms previous studies on ethnic/racial differences in both incidence and severity of hypertension.[3,4] In addition, all these data also brought up an important concern about the role of ethnic/racial and geographical variation in the nature of genetic predisposition to human diseases.[5]

It is well known that hypertension is a multifactorial disease. Many studies have shown that adjustment for lifestyle factors could not fully explain the ethnic/racial and geographical differences, indicating that many undiscovered factors contribute to the pathogenesis of hypertension. A large number of association studies have been conducted to investigate risk factors for hypertension; however, the results have been inconsistent, suggesting a high inter-population heterogeneity and phenotype complexity. Although the reason for the heterogeneity and complexity is not yet clear, it may be attributed to both environmental and genetic factors. The phenotype, therefore, is determined by the sum of multiple genetic and environmental factors. The gene–environment[6,7] and gene–gene interactions (epistasis)[8,9] modify the main effects of the causal genes. The complex interactions between genetic and environmental factors and the crosstalk between different regulatory pathways may have an important role in the pathogenesis and progression of hypertension and other common diseases.[10]

Recent advances in genetic analysis technologies have enabled the discovery of gene variants that contribute to the development of common diseases, including hypertension, diabetes and cancer. Unlike traditional linkage analysis and candidate gene association studies examining the effects of a few individual single nucleotide polymorphisms, genome-wide association studies are a powerful strategy for simultaneously identifying gene variants that are implicated in the susceptibility to common diseases. As no assumptions are made in advance about the genomic location of the gene variants, genome-wide association studies could serve as an unbiased and comprehensive approach to uncovering the causal gene variants.[11–13] Now it has been estimated from the results of the International HapMap project (http://www.hapmap.org)[14–16] and 1000 Genomes Project (http://www.1000genomes.org)[17] that there are millions of single nucleotide polymorphisms in the human genome. If insertions and deletions are included along with single nucleotide polymorphisms, the genomes of different individuals differ by about 1∼3%. As the frequency of gene variants (particularly ethnic/race-specific alleles) underlying human diseases can vary substantially among different ethnic/racial groups, the identified gene variants may be responsible for genetic susceptibility to common diseases. Of note, most of the individual genetic variants will generally have modest effects (odds ratio near 1) on disease risk. The combination of those individual genetic variants, however, will have a profound effect on the genetic predisposition to common diseases.

A comprehensive approach to understanding complex diseases is genome resequencing in large populations. Using next generation high-throughput sequencing techniques, the cost of sequencing has fallen greatly (currently $<$\$1 per million base pairs). This incredible progress has made genome-wide studies feasible. A systems biology approach will significantly advance our understanding of common genetic variants in complex diseases. Although a full understanding of the genetic basis of complex diseases cannot be reached quickly, it is anticipated that these types of progress will further our understanding of the genetic basis of complex diseases, leading to novel insights into the underlying gene regulatory networks.

The emerging challenge faced by biomedical researchers is to make the genetic association studies relevant to public health. The main goal of future genetic association studies of complex diseases is to focus on pathways relevant to these diseases that could reveal new therapeutic targets. For example, the genetic variants influencing responses to anti-hypertensive drugs could become a hot area of pharmacogenetics studies. By focusing on the genetic variants that have been discovered, we will understand better the variations across different ethnic/racial groups in the prevalence and severity of complex diseases, including hypertension, diabetes and cancer. Such an understanding will provide an opportunity to develop novel strategies for the improvement of healthcare for every ethnic group and for each individual. In the future, patients will be categorized by the genetic variants they carry, and different drugs and therapeutic strategies will be chosen for different patients. It is anticipated that 'personalized medicine' will soon become a routine healthcare paradigm.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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