Neglect of Several Important Indexes During the Study of Human Essential Hypertension

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Essential hypertension (EH) is both a multifactorial and a polygenic disease. Formally, there are two types of important factors, genetic and environmental, that can promote the development of EH.[1] Many clinical and experimental studies have substantially identified possible mechanisms underlying the development of EH, including increased activity of the sympathetic nervous system, overactivity of the renin-angiotensin aldosterone system (RAAS), dysfunction of the vascular endothelium, impaired platelet function, thrombogenesis, vascular smooth muscle and cardiac hypertrophy, altered angiogenesis, and miRNA deregulation.[2] However, these findings only partially explain EH. The Human Genome Project, the International HapMap Project, and the development of molecular genetics have sparked new interest in elucidating the genetic mechanisms underlying EH. However, although hundreds of hypertension-related genes have been identified and some genome-wide association studies (GWAS) have produced interesting results, only 1% of blood pressure (BP) changes can be explained by GWAS.[3–5]

One prominent use of GWAS is to identify genetic variants associated with common diseases and complex traits.[6] However, these studies have not provided much information regarding the genetic mechanisms underlying EH. This may be because EH is a multifactor and multigenetic disease, and its progression is affected by many environmental and genetic factors. Typically, for any particular trait, the cumulative effects of multiple single nucleotide polymorphisms explain only a small fraction of each individual's risk for the trait. Some scientists argue that the methods used for analysis are not necessarily reasonable, only common variants are detected in a given population (>5%), rare variants are untested, or gene-gene and gene-environment interactions are not estimated.[7] However, these may not be the key reasons why GWAS have failed in the study of EH. Other very important characteristics of GWAS relevant to such investigations are discussed below.

First, the age of the individuals included in the normotensive and hypertensive groups used in previous studies is questionable. In almost all the GWAS studies about EH, participant age was within the range of 18 to 70 years.[8–10] People of different ages are often engaged in different occupations and live in different environments. They also have different personalities; therefore, a man in his 20s may engage in more exercise and have less stress than a man in his 40s, which may have different effects on BP. People also have different genetic predispositions to hypertension. As age increases, people gain more risk factors for EH. These risk factors affect BP continuously and cumulatively. Many studies have shown that more people develop EH in older age than during youth or middle age.[11] It is difficult to tell whether normotensive young people will develop EH in their later years, which makes the selection of participants for normotensive control groups problematic. In most previous studies, each such control group can be assumed to contain both normotensive individuals who will later develop EH at some point and normotensive individuals who will remain normotensive. This places the accuracy of the results in jeopardy. The results of GWAS studies that use young men in their normotensive control groups should be questioned, even if the data are corrected for age. Age limitations may be a necessary criterion for the selection of normotensive or hypertensive populations during EH-related studies.

Some important environmental factors that can affect BP have not been considered in many studies on the mechanisms of EH. Stress, smoking, drinking, air pollution, physical and mental abuse, diet, and exposure to toxins, pathogens, radiation, and chemicals can all affect BP.[12,13] Every EH and normotensive patient is exposed to different environmental factors. Because EH is a polygenic and multifactorial disease, if environmental factors are not fixed, then the genetic factors cannot be well studied. However, in studies of EH, actual environmental factors were not given sufficient consideration. Some factors were considered, many more were not, and some were merely listed and subjected to overly simple analysis.[14–16] Studies that do not take important factors that can affect BP into account are less likely to produce reliable results. Therefore, more environmental factors should be taken into account in the study of EH. However, some types of environmental information may not be accessible. Because sample size is not always large enough to allow differences in environmental factors to average out, measures must be taken to keep environmental factors as similar as possible for every participant. This may help allow researchers to draw more reliable conclusions.

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Manuscript received: April 15, 2013; **revised:** May 9, 2013; **accepted:** May 19, 2013
DOI: 10.1111/jch.12156

Because EH is a chronic progressive disease, time is an important index in its development. During the initial phase, environmental, genetic (gene expression), and compensatory factors are completely different from later phases. In clinical practice, a 40-year-old man with a 1-year history of hypertension differs significantly from a 40-year-old man with a 10-year history.[11] In similar environments, the earlier the development of EH, the more severe the genetic predisposition.[8–10] However, almost all GWAS studies of EH have considered only the age of the participants at the time of the study, and the age of onset of EH has been left unrecorded and unanalyzed. If the onset and the duration of EH are not considered, then the results cannot reflect the true genetic susceptibility of EH patients. Therefore, the onset and the duration of EH should be recorded and analyzed.

Most studies have been performed on inadequate sample populations. GWAS have included thousands of EH patients and normotensive control participants, but this may not have been enough. So far, results instill little optimism. As it is known, genetic and environmental factors are important risk factors for EH development. If only genetic and environment factors are considered, and if there are 10 genetic factors and 10 environmental factors that can result in EH, there are 1,046,529 [[C(10,1) + C(10,2) + …… + C(10,10)] × [C(10,1) + C(10,2) + …… + C(10,10)]] = 1023 × 1023)] possible combinations of risk factors. According to a 4-dimensional model of the mechanism of EH, time factors (including age and duration of EH) and compensatory factors are also determinants of EH, and the number of risk factor combinations is very large.[17] For this reason, although some GWAS have screened thousands of patients,[3,4] perhaps even those samples are too small to produce useful results. Larger sample sizes and stricter criteria are needed.

Compensatory factors, here defined as some definite vasoactive factors that regulate BP, the ability of the human body to regulate BP, the process of BP regulation, and other unrelated factors have not always been considered and separated from causal factors.[17] Some genes can increase the risk of EH, other genes can lower BP, and yet some are not related to EH at all. For example, the concentration of angiotensin II (Ang II), a vasoconstriction polypeptide, is increased in plasma of EH patients.[18] That of ANP, a vasodilatory polypeptide, is also increased in plasma of EH patients.[19] However, the concentration of endorphins, which are unrelated to hypertension, are also increased in the plasma of EH patients.[20] Increases in the concentration of Ang II may be part of the primary etiology of EH. Increases in ANP secretion (or other BP-lowering signals) may be a compensatory factor that helps lower BP. Increases in endorphin levels may be caused by stress and are probably not a risk factor for EH. Hundreds of these factors have been found in the plasma of EH patients. If these factors are not distinguished from each other by their functional traits, they can conceal the true mechanism of EH and may result in unexplainable results. Unfortunately, however, these factors have not been well distinguished and categorized during EH studies and GWAS. For this reason, the results of EH studies, including GWAS, are of limited usefulness.

In total, EH is a multifactorial and polygenic disease. Environmental and genetic factors may affect the development of EH. Compensatory factors decided by genetic factors can also regulate BP. What's more, EH is a chronic and progressive disease. For these reasons, GWAS and other genetic studies must take into account all factors that may affect BP. Confounders must be excluded or keep similar in the studied participants to the greatest extent possible. Then the effects of genetic factors may become more visible, and genetic studies may provide reliable results.

Acknowledgments and disclosures: This work was supported by grants from National Natural Science Foundation of China (No.81270216) and Beijing Natural Science Foundation (No.7102045, 7120001). The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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