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COMMENTARY

Quality over quantity? No, quality and quantity

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Most researchers in genetics would agree that essential hypertension is one of the toughest multifactorial diseases to tackle. There are two main reasons for such difficulty. First, it is cumbersome to obtain reliable measurements of the target phenotype, blood pressure (BP). BP shows much quicker and larger fluctuations than do other phenotypes (for example, blood glucose level). Second, after many genetic studies, we have realized that genomic variations making up the genetic susceptibility to hypertension seem to be much broader than previously expected. Even worse, single genetic variations have very small effects and may have complex interactions with other genes and environments. This has been suggested in both rats and humans. Results of large-scale genome-wide association studies (GWASs) recently published indicate that the association of each single nucleotide polymorphism (SNP) with hypertension is quite weak. Indeed, it may require a huge number of SNPs to explain the total genetic variance of BP, if the effects of such SNPs are assumed to be additive.[1–3] In rats, we have clear evidence that quantitative trait loci for BP show asymmetrical effects depending on the genetic background, implying gene–gene interactions among the separated genomic regions.[4,5] The present genetic studies on hypertension, therefore, must address all of these problems.

A report by Watanabe *et al.*[6] in this issue of *Hypertension Research* is surely one such study. This study is unique in that it uses 'home BP' as a target phenotype. As BP was measured repeatedly by participants themselves at home, it should be reliable and free from any influence of 'white-coat syndrome' or other biases. In addition, this study employed a prospective study design, which is generally thought to be the most reliable epidemiological study design for inferring causal relationships. The authors measured the home BP of the same participants under the same setup after an average follow-up period of 12 years, which allowed them to compare BP changes in the same subject over time. In this study, therefore, the effort was focused on obtaining reliable phenotypes.

Under these study conditions, the authors evaluated the effects of 51 SNPs on the development of hypertension. They identified four SNPs showing a statistically significant association ($P<0.05$) with the development of hypertension. These SNPs had additive effects on the relative risk of hypertension, which resulted in a 10 times greater risk when all four risk genotypes were combined.[6]

As noted by the authors, however, the most serious problem in the study is lack of statistical power. In exchange for the intensive phenotyping, the number of subjects was limited. It is but natural that most researchers would agree that it is ideal to monitor the home BP of tens of thousands of subjects in GWASs; this would provide more reliable genetic analysis of hypertension. At the same time, however, it is unclear who would be able to obtain such a collection of samples. Owing to the daunting nature of taking such a complicated measurement from thousands of participants, we cannot blame the authors of the present study for the small size of the population. Instead, we point out that it may have been better to select an appropriate number of SNPs in their analysis to improve statistical power.

Another problem related to phenotype in the study by Watanabe *et al.* centers on the fact that BP data were reduced to a dichotomous phenotype in the screening of the 51 SNPs. This may result in the loss of valuable information from the original data. Furthermore, according to the criteria employed in the study, a subject with an increase in BP from 129 to 131 mmHg was categorized as a 'case'; in contrast, a subject experiencing a BP increase from 100 to 129 mmHg was classified as a 'control'. This is, of course, an extreme argument, but the fact that the baseline BP was substantially greater in the 'case' group raises some concerns (Table 1 of Watanabe *et al.*[6]). By nature, the home BP metric includes many data points. It is necessary to establish a strategy for using them properly in the analysis.

This study was designed as a replication of candidate SNPs identified in a previous study.[7] However, we have to be cautious when interpreting the results. Although the authors excluded 47 of the 51 SNPs examined in this study, we cannot exclude the genes harboring these SNPs instantly for the following reasons. First, the SNPs were more or less arbitrarily selected from the physiological candidate genes of the previous study.[7] Accordingly, they are neither necessarily functional nor tagged SNPs in nature, and thus, the genes may have other SNPs associated with hypertension. Second, the phenotype was not exactly the same as that in the previous study (home BP versus ambulatory BP). Third, a population with a different property was employed in this study. As noted by the authors, participants in this study were normotensive at the baseline, when their average age was in the mid-50's (Table 1 of Watanabe *et al.*[6]). These conditions differ from those in the previous study and may be responsible for the discrepant observations between the studies.

As mentioned above, hypertension is the toughest multifactorial disease to address

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from the genetic point of view. In the first comprehensive GWAS by the Wellcome Trust Case Control Consortium, hypertension was the only disease among the seven common diseases studied that showed no significant SNP associations.[8] Two years later, a substantial scale-up of the study managed to identify some SNPs associated with hypertension.[1,2] Under the current situation, therefore, what remains to be done? First, it is necessary to perform a GWAS in Asian populations. So far, most GWASs have been conducted in Caucasian populations, and the lack of information regarding Asian populations is obvious. The largest association analysis performed in Japan was one by Kato *et al.*[9] using 1500 cases and 3600 controls with 80 000 J-SNPs. A cross-sectional study using 8800 subjects and a case–control study using 1200 cases and 1200 controls were performed in Korea and in Taiwan, respectively.[10,11] It remains a subject of debate whether the Japanese Society of Hypertension will take the initiative to organize a larger-scale GWAS in Japan.

Progress in genotyping technology has been made quite rapidly. Accordingly, '$1000 sequencing', in which the whole genome sequence of one person will be finished within a few days at a cost of $1000, will soon be realized. By constrast, technologies for phenotyping do not progress as rapidly. Phenotyping still requires substantial labor, time and cost. In the post-GWAS era, however, we have to tackle the more difficult task of resolving gene–gene and gene–environment interactions. To achieve this goal, collecting reliable phenotypes and complete and reliable information about environmental factors from thousands of subjects will be key issues. Such work may not be glamorous, but it is certainly essential.

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