Editorial Comment

Large-Scale Candidate Gene Approach to Identifying Hypertension-Susceptible Genes

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(*Hypertens Res* 2008; 31: 173–174)

***Key Words*: hypertension, candidate genes, genetics, pathway for hypertension**

In 1999, the Japanese government announced that it was going to initiate a top-down, 5-year mega-initiative for genome analysis, the Millennium Genome Project. This initiative aimed to establish genome-based personalized medical care and to develop genome-based method for drug discovery. The project consisted of five teams, including a "Disease Gene" team to analyze five so-called common diseases: dementia, cancer, diabetes, asthma, and hypertension (*1*). A consortium was organized for each disease, under which a Hypertension Consortium was established for genetic analysis in hypertension research in Japan. The Hypertension Consortium adopted two approaches for hunting hypertension-susceptible genes: a hypothesis-driven candidate gene approach and a genome-wide association approach (*2*). One achievement of the candidate gene approach appears in the present issue of *Hypertension Research* (*3*). The latter will appear elsewhere soon.

As is well known, hypertension is etiologically multifactorial. Lifestyle factors, including high sodium intake, drinking, and excess weight can elevate blood pressure. Genetic factors are also important for blood pressure. In this issue, Kohara *et al*. took the candidate gene approach to identifying hypertension-susceptible genes and pathways (*3*). To achieve this goal, they adopted a sophisticated and elegant strategy using pathway-oriented selected genes and two-stage association design. They first selected candidate genes that might be related to blood pressure regulation, encoding the components of signal transduction systems including enzymes, channels, receptors, solute carriers, G-proteins, and binding proteins. Other genes of particular interest, such as collagens, growth factors, adhesion molecules, and hormones, were also selected as candidates. Next, they searched for single nucleotide polymorphisms (SNPs) in each candidate gene using the publicly available JSNP database (*4*). They selected one SNP in each gene, preferably in the promoter region or in exons with the highest minor allele frequency in the Japanese population. Finally, they genotyped 307 such SNPs in 307 genes in hypertensive patients ($n=758$) and normotensive controls ($n=726$) that had been collected from four institutions in Japan. In total, 38 SNPs, including five G-protein–related genes, were positively associated with hypertension. To replicate the results for the G-protein–related genes, they genotyped them in the second panel, consisting of 3,305 hypertensives and 3,827 normotensives recruited from five cohorts, and finally identified two genes: GNA14, a guanine nucleotide binding protein (G-protein) α14, and RGS20, a regulator of G-protein signaling 20, as hypertension-susceptible genes.

GNA14 is one of the α subunits of G-proteins that are trimeric membrane-associated proteins. G-proteins link G-protein–coupled receptors such as β-adrenergic receptors and adenylyl cyclase, and regulate the flow of information from cell surface receptors to a variety of internal effectors. RGS20 is one of the RGS proteins that negatively regulate G-protein–coupled receptor signaling pathways by enhancing endogenous GTPase activities of G-protein α subunits. Thus, both GNA14 and RGS20 proteins are supposed to be involved in the signal transduction pathway of G-protein–coupled receptors. However, the lack of a detailed understanding of the biochemical characteristics of G-protein–coupled receptors for both proteins hampered elucidation of the possible mechanisms by which these proteins regulate blood pressure regula-

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Received November 28, 2007.

tion. The *in vivo* functions of both GNA14 and RGS20 are not well understood. Neither are the effects of the SNPs of these genes. To reveal the relationships between these genes and blood pressure regulation, further intensive studies including transgenic or knockout animal models are necessary.

The year 2007 was the year of the genome-wide association study. The genetic backgrounds of common diseases were examined as part of the large-scale genome-wide association study, and several reports were published in 2007. In the United Kingdom, the Wellcome Trust Case Control Consortium has studied seven major diseases, including hypertension, as part of the genome-wide association study using ~2,000 patients with each disease and ~3,000 controls (*5*). That large-scale case-control study identified strong association signals in several SNPs for diseases including bipolar disorder, coronary artery disease, Crohn's disease, rheumatoid arthritis, and types 1 and 2 diabetes, but not for hypertension. For hypertension, none showed a strong association, and only six SNPs showed moderate associations. In the Framingham Heart Study, a genome-wide association study for hypertension again failed to detect the strong signals (*6*). There are several possible explanations, including fewer risk alleles of larger effect sizes, poorly tagged SNPs genotyped in the study, and misclassification bias due to the presence of hypertensive individuals within the control samples. Genome-wide association studies cannot discern rare variants or extra copies of genes that can have strong effects on the protein function.

Taken together, these findings indicate that the identification of hypertension-susceptible genes is still on the way and that more effort is required for the assessment of these genes in blood pressure regulation. A second generation of the human haplotype map has been published (*7*), and the dbGaP (database of Genotype and Phenotype) public repository for individual-level phenotype and genotype data, as well as the associations between them, has been created (*8*). The necessary tools and evidence in this field are accumulating.

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