Genome-Wide Association Studies Will Unlock the Genetic Basis of Hypertension

Con Side of the Argument
Theodore W. Kurtz

Abstract—Over the past few years, it has been asserted that genome-wide association studies would open the door to identifying primary genetic mechanisms underlying a variety of common clinical disorders, including essential hypertension. Great hope was expressed that such research would ultimately lead to improved clinical outcomes by facilitating the discovery of novel targets for therapy and by spawning a new era of personalized medicine in which the results of genetic tests would be useful for guiding customized risk assessment and individual patient management. In this Controversies in Hypertension series, I contend that genome-wide association studies have failed, and will continue to fail, to unlock the genetic basis of essential hypertension and the research dollars being devoted to genome-wide association studies should be shifted to other strategies and technologies that may hold greater chance for advancing our understanding of the genetic factors that influence population variation in blood pressure and risk for hypertension. (Hypertension. 2010;56:1021-1025.)

Key Words: genetics ■ hypertension ■ genome ■ association studies ■ blood pressure

What Have We Learned So Far About the Genetic Basis of Hypertension From Genome-Wide Association Studies?
The proponents of genome-wide association (GWA) studies assert that such research has already provided initial insights into the genetic basis of hypertension and that larger genome-wide studies are warranted in the future.1,2 I disagree with both assertions. To see that we have learned very little about the genetic basis of hypertension from the large genome-wide association studies conducted to date, it is helpful to consider what the results of GWA studies have actually shown so far and what was known about the genetic architecture of hypertension before the advent of GWA studies. I then discuss why little is expected to be gained by more GWA studies of hypertension in the future.

Disappointing Results From the Largest GWA Studies Relevant to Hypertension
Recently, the results of several large GWA studies relevant to hypertension have been reported, including 2 that each involved analysis of 2.5 million genetic markers in ≈30 000 individuals.1,2 In both cases, only a few loci (chromosome regions) were found to be associated with effects on blood pressure (BP) at a genome-wide level of statistical significance. The implicated loci had only tiny effects on BP (<1 mm Hg or so) and typically accounted for <0.2% of the overall BP variation in the study populations. In the Gobal BPgen consortium study, investigators selected genetic markers for 10 of their loci and subjected them to analysis in 134 258 subjects from 35 studies. The results of this effort yielded 8 loci that met criteria for genome-wide significance. Again, each of these loci was associated with miniscule effects on BP, with each accounting for <0.1% of the total variation in BP.

Did These GWA Studies Lead to Any Surprising Conclusions About the Genetics of Hypertension?
Unfortunately, the results from these GWA studies have told us little if anything new about the genetic architecture of
hypertension (Table). They have not unlocked the genetic basis of hypertension, nor are such studies likely to do so in the future. Based on the results of the main GWA studies of hypertension conducted to date, the authors merely concluded what everyone already knew about the genetics of hypertension before the advent of GWA studies, that essential hypertension is a polygenic disorder in which multiple genetic variants are involved in the regulation of BP. Specifically, the investigators of the Cohorts for Heart and Ageing Research in Genome Epidemiology consortium concluded that, “The findings are consistent with the hypothesis that variation in scores, if not hundreds, of genes contribute to BP variation”\(^1\); the Global BPgen investigators concluded that, “Given the modest effects observed here and the limited power of this study to detect such effects, it is likely that many more common variants exist with weak effects on blood pressure.”\(^1\)

**GWA Studies Have Not Addressed and Cannot Address the Key Question Regarding the Genetic Architecture of Hypertension**

It has long been accepted that essential hypertension is a polygenic disorder. What has been unclear is whether genetic risk for essential hypertension is determined to a greater extent by many common gene variants with individually small effects on BP (the common disease–common variant model) or by many different rare gene variants with individually large effects on BP (the common disease–rare variant model).\(^5\) The GWA studies conducted to date have shed little light on the relative roles of these 2 models in the pathogenesis of hypertension, and more GWA studies will not be able to clarify this issue much further in the future.

By nature of their design, GWA studies are intended to detect the effects of common gene variants on BP and have limited ability to detect rare variants affecting BP.\(^4\) Gene variants with minor allele frequencies between 5% and 50% are considered common, those with minor allele frequencies of 1% to 5% are considered less common, and those with minor allele frequencies of <1% are considered rare.\(^5\) The fact that GWA studies have turned up so few candidates in the search for common gene variants influencing risk for hypertension might suggest that rare gene variants are playing a greater role than common gene variants in the genetic architecture of hypertension.\(^5\) To the extent that this ultimately proves to be true, investigators involved in GWA studies of hypertension have been “barking up the wrong tree.”\(^6\) Recently, prominent geneticists have begun to argue that rare variants might play a much more important role than common variants in the pathogenesis of a wide range of common clinical disorders, including essential hypertension.\(^5\) **Claim 1: Small Effects on BP Can Have Meaningful Effects on Cardiovascular Risk**

The largest GWA studies conducted to date identified common genetic variants that appeared to impart only tiny effects on BP.\(^1,2\) However, the study investigators emphasized that even very small changes in BP can “produce meaningful population changes in cardiovascular and stroke risk.”\(^2\) It may well be true that, if a reduction in systolic BP of 1 to 2 mm Hg could be achieved across the entire population, it would translate into a meaningful reduction in coronary heart disease and stroke in the population. However, this has no relevance to the potential clinical importance of genetic variants implicated in GWA studies, because no one is going to manipulate genetic variants across the entire population.\(^8\) Imagine if a clinical trial demonstrated that a new antihypertensive drug could reduce BP by only 1 mm Hg. In the context of such a clinical trial result, it would make no sense to note that a 1-mm Hg reduction in BP across the entire population could translate into a meaningful reduction in cardiovascular risk in the population, nor does it make sense to note this issue in the context of a GWA study of hypertension. The fact that a 1-mm Hg reduction in BP across
the population can have a meaningful impact on population cardiovascular risk does not mean that discovery of an antihypertensive drug that lowers BP by 1 mm Hg, or discovery of a group of genetic variants that affect BP by 1 mm Hg, holds any clinical significance.

Claim 2: GWA Studies Can Yield Mechanistic Insights Into the Regulation of BP By Identifying Causal Genetic Variants for Hypertension

Proponents of GWA studies of hypertension have claimed that, “These associations between common variants and BP and hypertension can offer mechanistic insights into the regulation of BP.” However, mechanistic insights can be gained only by identification of the true culprit gene variants influencing risk for hypertension and not by identification of candidate genes. GWA studies can suggest candidate genes for hypertension but they do not prove identity of the true causal genetic variants that are required for investigators to gain mechanistic insights into regulation of BP. The Global BPgen investigators admit that GWA studies of hypertension only identify candidate genes and that they do not pinpoint the true causal genetic variants: “Although we describe promising candidates at each locus identified, the causal genes could be any of the genes around the association signal in each locus.” Even higher-resolution GWA studies cannot establish proof of causation for a specific gene variant in hypertension. Moreover, even if GWA studies succeed in identifying valid candidate genes as opposed to false candidates implicated by spurious association results, one need only peruse a few issues of Hypertension to realize that there is hardly a shortage of candidate genetic pathways for BP regulation in the field of hypertension research.

Claim 3: GWA Studies Will Lead to Identification of Important New Targets for Treatment of Hypertension

This claim stems from the idea that, by identifying candidate genes that affect risk for hypertension, GWA studies will help uncover new pathways influencing BP and “serve as a basis for the development of novel therapies for the prevention and treatment of hypertension.” While recognizing that many if not most of the candidates implicated in GWA studies of common disorders like hypertension could represent spurious associations, let us again assume for purposes of discussion that the candidates identified by the Cohorts for Heart and Ageing Research in Genome Epidemiology and Global BPgen investigators are valid. Proponents of GWA studies note that a common variant in the gene encoding 3-hydroxy-3-methylglutaryl-coenzyme A reductase was found to be associated with only a modest effect on fasting lipid levels, yet statin therapy, which inhibits 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity and lowers cholesterol levels, is effective in lowering the risk for cardiovascular disease. Of course, GWA studies were not required to discover the important role of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and statins in regulating cholesterol levels. The GWA studies of lipid levels are cited to support the possibility that other GWA studies might lead to a therapeutic target for hypertension that is as important as 3-hydroxy-3-methylglutaryl-coenzyme A reductase has been for hypercholesterolemia. However, given that the very large GWA studies relevant to hypertension have failed to show associations with any of the known targets used for treating hypertension in the clinic today, there seems little reason to expect that GWA studies will be useful for detecting any important therapeutic targets in the future. Moreover, the field of hypertension is not lacking in candidate targets for therapy, and there is no evidence that candidate targets for therapy identified in GWA studies will be any more useful than candidate targets identified through other approaches.

It is unquestioned that a focus on rare gene variants promoting mendelian forms of cardiovascular disease is of value in understanding mechanistic pathways that serve as useful targets for therapeutic intervention. The genetic studies of mendelian forms of disordered BP regulation readily turned up targets that are of known relevance to the treatment of hypertension. The same cannot be said for the focus on common gene variants that are reported to be associated with tiny effects on BP. Judging from failure of the large GWA studies to uncover associations with most if not all of the target pathways for antihypertensive therapy that have already been established, why should we bet on this approach to discover any special target pathways for antihypertensive therapy in the future?

Claim 4: The Results of GWA Studies Will Lead to Development of Genetic Profiles That Are Useful for Predicting an Individual’s Risk for Hypertension

The simplistic concept of using the results from GWA studies to develop genetic profiles to predict an individual’s risk for developing complex disorders like hypertension is going out of favor. These kinds of results have very limited value for personalized risk prediction, because in complex multifactorial disorders like essential hypertension, the relationship between genotype and phenotype (BP) is very weak. Nevertheless, some investigators continue to suggest that the results of GWA studies of hypertension “can serve as a basis for future approaches to early detection of high risk individuals.” For example, the Cohorts for Heart and Ageing Research in Genome Epidemiology investigators created BP “risk scores” by aggregating the effects of the top 10 genetic markers implicated in their GWA studies and showed that subgroups with the highest risk scores had the highest odds ratios for hypertension. It should be noted, however, that the odds ratio for hypertension in the group with the highest risk score was at best = 1.5. From the perspective of predictive testing in an individual, an odds ratio of 1.5 is of practically no value. In fact, even if every genetic factor involved in hypertension could be identified and analyzed, the accuracy of genetic profiling would not be any better than simple clinical risk scores in predicting who will and who will not get hypertension. This is because of the fact that a very large fraction of BP variation is determined by nongenetic factors. Some might suggest that we should attempt to unravel the BP impact of gene-gene interaction and gene-environment interaction in hopes of further improving the discriminative ability of risk profiling based on common variants with apparently small effects on BP. However, assuming such studies were technically feasible to begin with, they would be extremely...
expensive and not worth the effort for the reasons discussed below.

Even if one could develop a better risk score with high discriminative ability, there is little rationale for early detection of individuals at high risk for essential hypertension. It is unclear whether patients who are given information on their genetic risk for hypertension will be any more likely to adopt appropriate lifestyle changes and reduce their risk for hypertension than patients not given such information. Moreover, recommendations for preventing essential hypertension, including control of body weight, dietary habits, stress, physical exercise, alcohol intake, and tobacco intake can be helpful for everyone, not just people with increased risk for hypertension. Such recommendations can and should be made regardless of an individual’s estimated risk for hypertension.

**Given the Limited Value of GWA Studies for Unlocking the Genetics of Hypertension, Is There a Better Way Forward?**

Although considerable effort has been expended on GWA studies to search for common genetic variants with individually small effects on BP, the attention of geneticists has recently begun to shift to the “rare gene variant” hypothesis for common disorders like hypertension. The fact that GWA studies have identified common genetic variants that together account for only a tiny fraction of complex trait variation in the population has stimulated some to suspect that the so-called “missing heritability” may be traceable to effects of rare variants that cannot be detected by GWA studies. As mentioned previously, the rare gene variant hypothesis holds that much (but not necessarily all) of the genetically determined BP variation in the population stems from a large number of different gene variants, each of which is rare in the population and each of which can individually exert relatively substantial effects on BP. Thus, although each individual variant itself may be rare, such rare variants could still play important roles in common disorders like hypertension because, throughout the population, there could be many different types of rare variants with individually strong effects on BP.

The best illustration of the potential role of rare gene variants in the pathogenesis of essential hypertension is found in a study of 3125 participants from the Framingham study performed by Lifton and colleagues in which they carefully sequenced 3 genes known to be involved in renal electrolyte transport and BP regulation. Previous studies by Lifton and colleagues had uncovered mutations in these genes that caused rare recessive diseases characterized by very large reductions in BP. Remarkably, 1 of every 64 subjects in this Framingham cohort was found to carry a mutation of potential functional significance in 1 of these 3 genes. Very few of the carriers shared the same variant in common (the tendency was for each person to carry his or her own particular mutation so that each specific mutation was rare). On average, the systolic BP at age 60 in those carrying one of these rare mutations was 9 mm Hg lower than in the noncarriers, and having one of these rare mutations reduced the risk for hypertension at the age of 60 years by ≈60%. It is important to keep in mind that this study examined just 3 genes. Thus, if one were to fully sequence the coding regions of many more genes relevant to known BP control pathways, it would not be surprising to find more individually rare variants of potential functional significance in many more people.

To investigate whether many individually rare gene variants play a major role in genetic susceptibility to essential hypertension, it will be necessary to find the variants and then somehow determine their effects on BP. Finding such rare gene variants will require sequencing large numbers of genes in many thousands of people. Thanks to radical advances occurring in DNA sequencing technology, it appears that comprehensive searches for rare gene variants are becoming more feasible. The task of finding rare gene variants will be easy compared with the task of determining which ones are actually influencing BP and risk for hypertension. Although it will be a challenge to clearly establish the impact of rare gene variants on BP and risk for hypertension, the work of Lifton and colleagues suggests some potential usefully ways to approach this problem in the future.

**Future Perspectives**

Although GWA studies have failed to unlock the genetics of hypertension, there is reason to hope that some of the next-generation research technologies and strategies being developed will prove to be more effective in this regard. Nevertheless, the ultimate clinical value of identifying many if not most of the DNA sequence variants, both rare and common, that mediate genetic risk for essential hypertension remains open to question. It has been argued that, because the individual phenotypic effects of rare gene variants are stronger than those of common gene variants, identification of rare gene variants could be of more practical clinical use than identification of common gene variants. However, for medical disorders like essential hypertension that are characterized by very high prevalence and where much of the risk is influenced by nongenetic factors, genetic profiles that incorporate rare variants with relatively large effects on BP may still not provide sufficient discriminative accuracy to make them very useful in clinical practice. It also remains to be determined whether identification of rare variants associated with increased risk for essential hypertension will lead to new insights into better methods for prevention or treatment of hypertension. Thus, even if the next-generation sequencing tools and analytic strategies prove to be more successful than GWA studies in unlocking the genetics of hypertension, it would seem prudent to avoid promoting these new research opportunities in the hyped up manner in which GWA studies were promoted in the past.

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**Disclosures**

None.

**References**

The future of genomics is bright, and the GWASs have been an important building block for a future success. The GWASs demonstrated, for the first time, that it is possible to study a million or more SNPs across the entire genome. Novel findings of mechanistic significance for many complex polygenic traits, such as coronary artery disease, diabetes mellitus, obesity, and many others have been established. Human essential hypertension is the most common treatable polygenic trait. It would have been negligent of us not to apply the new tools of genomics to improve our understanding of this disease.

What have we gained? I think we gained that both the common variant/common disease and rare variant/common disease hypotheses are needed to explain the genetic determinants of hypertension. The common variants identified as being associated with essential hypertension are currently a subject of further functional studies, which are likely to reveal new pathways and new drug targets. The rare variants similar to those studied by Lifton’s group are about to be revealed by the ongoing exome sequencing efforts, particularly where careful phenotyping and patient selection allow common pathways from rare phenotypes.

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