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Genome-wide association studies of hypertension: Achievements, difficulties and strategies

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Abstract

Estimated from family studies, the heritability of hypertension ranges from 31% to 68%. Linkage studies and candidate gene association studies were once widely used to investigate the genetic mechanisms of hypertension. However, results from these studies could only explain 1%-2% heritability. With the technological advances and subsequently the accomplishment of the Human Genome Project, genome-wide association studies (GWA studies) have been applied to find genome-wide significant signals for many common diseases. Current GWA studies of hypertension have identified dozens of hypertension or blood pressure associated variants. However, different GWA study identified different variants and the results could hardly be replicated in other studies. Therefore, a debate took place on whether GWA studies will unlock the genetic basis of hypertension and whether we shall continue throwing millions of dollars on GWA studies. This review gives a short introduction to the history of genetic study on hypertension and summarizes the current findings for GWA studies of hypertension or blood pressure. Finally, we will discuss that debate and try to find alternative strategies and technologies that may hold a greater chance to make progress in understanding the genetic risk factors of hypertension and blood pressure regulation.

Key words: Hypertension; Genome-wide association study; Achievement; Difficulty; Strategy

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INTRODUCTION

Genetic and epidemiological data have revealed that hypertension is a typical complex disease which arises from the interaction of polygenetic and environmental factors. For decades, scientists and cardiologists have known that the hypertensive traits are highly heritable. Estimated from family studies, the heritability of hypertension ranged from 31% to 68%[1,2]. Thereafter, multiple twin

studies showed that the heritability exceeded 50%, which indicated that more than half of the blood pressure variation could be attributed to genetic effects[3,4].

Family-based linkage studies were once widely used to investigate the genetic mechanisms of hypertension. They were quite successful in identifying the "hypertension causal gene"[5], but these genetic variants were not associated with hypertension in the general population[1]. Following this, many candidate gene-based and genome-wide linkage scans have been performed but none of these studies offered convincing results[6,7]. The main difficulty in identifying hypertension or blood pressure (HT/BP) associated genes is the low power of linkage study for variants with modest effects[8]. To compensate for the defect of linkage study, candidate gene association studies on HT/BP have been widely used. Hundreds of candidate genes have been examined, especially for genes involved in the rennin-angiotensin-aldosterone system and renal sodium transport system[9-11]. However, still not much progress has been made in candidate gene approach for hypertension and/or blood pressure.

ACHIEVEMENT

With the technological advances and subsequently the accomplishment of the Human Genome Project, we are able to genotype 1 million single nucleotide polymorphisms (SNPs) at a reasonable cost. Genome-wide association studies (GWA studies) have been applied to find genome-wide significant signals for many common diseases[12]. The GWA studies represent the first unbiased survey of disease-predisposition variants in the genome. Hypertension was one of the first diseases to be studied by GWA study. The first large collaborative GWA study for hypertension was completed by the Wellcome Trust Case Control Consortium and the results were published in 2007[13]. However, none of the SNPs passed the threshold of genome-wide significance established at $P < 10^{7}$ in this study. At least twelve further GWA studies for HT/BP have been published since then[14-25] (for details see review by Ehret[1]). Two large-scale meta-analyses of GWA studies for HT/BP were published in 2009[17,19]. These were CHARGE BP consortium and Global BP Gen consortium, each of which analyzed 2.5 million genetic markers in about 30 000 individuals. Among all the GWA studies on hypertension, only these two studies on blood traits have identified genome-wide significant loci and could be replicated in other studies. However, only one SNP reached the genome-wide significance for hypertension and several SNPs for systolic blood pressure and diastolic blood pressure. Moreover, these implicated that SNPs had only minor effects on blood pressure (less than 1 mmHg) and accounted for no more than 0.2% of the overall blood pressure variation in the study population[26]. GWA study can be used to make a bright future for indentifying the genetic mechanisms of hypertension, which ultimately would be useful for early intervention for susceptible people and individual patient management. However, after 13 GWA studies, the results are quite disappointing.

CONTROVERSY

Can GWA studies unlock the genetic basis of hypertension? Shall we continue throwing millions of dollars on GWA studies? Or shall we shift the research strategies and technologies that may hold a greater chance to make progress in understanding the genetic risk factors of hypertension? Recently, "Hypertension" published a debate that took place in an annual meeting in May 2010. The pro side representatives described the success of recent work, including 13 SNPs associated with HT/BP at $P < 5 \times 10^{-8}$. They also suggested a way forward, including resequencing using next generation sequencing technologies to aid fine mapping and the identification of causal variants, even bigger meta-analyses and developing appropriate functional studies to take way from GWA studies and related methodologies to useful clinical applications[27]. In the controversy, the con side representatives contended that GWA studies have failed in hypertension studies. Only 13 associated SNPs were found and few of them could be successfully replicated in follow-up studies. They suggested that research efforts and dollars should be shifted to other strategies and technologies that may hold a greater chance in advancing our understanding of the genetic factors that influence population variation in blood pressure and risk for hypertension[26].

STRATEGY

Despite the different opinions, we still have to admit that the findings of GWA studies are an encouraging step in hypertension genetics because they open the way for subsequent investigations. It is also believed that one of the biggest gains from GWA studies is the expansion of the pathophysiology of hypertension. As in most cases, genes and regions identified are novel and fill critical gaps in our current knowledge. Moreover, a common non-coding SNP discovered might have a small effect, but the underlying gene/protein/pathway might become a very important target. Therefore, we should reconsider the research strategies according to the problems we have met.

Firstly, more homogeneous samples should be involved in GWA studies. Linkage study and the candidate gene approach have failed because of their low power to indentify variants with modest effects. Given the effective sizes observed and the number of tests performed, the power is still low, even in a GWA study with 30 000 individuals[1]. The International Consortium for Blood Pressure is organizing and will combine all of the cohorts from the Global BPgen and CHARGE with some additional cohorts and present data from > 70 000 participants[28]. Large-scale cohorts to study blood pressure traits in nonwhite populations (such as the Korean Association Resource, Chinese Han GeneID) are under way. Further meta-analysis with larger sample size would be

more widely used for the evaluation of the evidence.

Secondly, more ethnic populations should be considered in future studies. Our group have selected dozens of "hypertension-associated SNPs" from the above mentioned GWA studies and completed the replication study in the Han Chinese population but only one or two SNPs could be replicated in our own study (data not shown). It suggests that ethnic difference might be a great challenge in GWA studies. Several different ethnic populations have been examined in GWA studies but it has mostly focused on Europeans. This is mainly due to the well prepared European origin samples but it is also a great challenge to study Africans because of the complex recombination. Among 13 studies, only one was done on the Han Chinese population[24]. In 2009, Chinese Ministry of Science and Technology launched an 863 project of GWA study to identify the association between variants and hypertension in the Han Chinese (http://program.most.gov.cn/htmledit/UploadFile/20090310112521187.doc). To our knowledge, Hong Kong researchers are also carrying out GWA study in the Han Chinese. The more ethnic populations we study, the more useful information we get.

Thirdly, discoveries from GWA studies are inherently limited to common variants as a result of microarray design. Thus, rare variants (minor allele frequency < 5%) might be a more important source of "missing" heritability[29]. A good example of the potential role of rare variants in the pathogenesis of hypertension is found in Framingham Cohort study performed by Lifton and colleagues[29] in which they sequenced 3 genes and found 1 of every 64 subjects in the study carrying a mutation with potential function in 1 of these 3 genes. If more genes are sequenced in many thousands of people, it would not be surprising that more rare variants would be identified. For low allele frequency, the sample size should be carefully considered before we get reliable variants, and customized microarray should be used in later GWA studies. Thanks to quick advances in high-throughput DNA sequencing tools and analytic strategies, it appears that comprehensive searches for rare variants are becoming more feasible[30]. Thus, next-generation sequencing might take the part of GWA studies in future studies, which have been proved to be more successful in unlocking the genetics of hypertension[26].

Fourthly, recent genome-wide significant variants are often merely tag but without direct information on their functions. Classical cell-line reporter assays for *in-vitro* examination of the cis-regulatory effect of SNPs were usually used in the times of candidate gene approach; however, its throughput could not meet the needs now. Bioinformatics methods provide a chance to identify regulatory function of thousands of variants. Tang and colleagues developed the mixed linear model approach to examine the variance of genetic expression in the HapMap lymphoblast cell lines[31]. A simple extension to include fixed effects due to SNP genotypes within a window of certain distance into the model will demonstrate if particular candidate SNPs have a cis-effect on gene expression. Fine mapping sequencing or custom-made microarray approaches, together with ChIP-on-chip technology, will be widely used in future studies, not only to get a better estimate of the real effects on phenotype, but also to translate these signals to biological functions and clinical applications.

Finally, hypertension and blood pressure have been considered complex genetic traits since the classic work of Pickering and colleagues[32]. Before the era of GWA studies, epidemiological studies have found dozens of risk factors, such as smoking, alcohol abuse, excessive salt intake, obesity, mental stress, *etc*. It is widely believed that gene-environment interactions play an important role in the pathogenesis of hypertension but it is not currently possible to quantify them. The participants in recent GWA studies are mainly from well-organized cohorts (Global BPgen and CHARGE), which means the epidemiology data are available. With the development of statistical methods for evaluation of gene-environment interaction, more missing inheritability will be found.

CONCLUSION

GWA study for the first time permits us to study most common variants in the human genome. Application of this technology to BP/HT traits has identified dozens of associated variants and contributed to a better understanding of BP regulation. However, current limitations of GWA studies impede the further findings and, thus, research strategies should be changed. Taking into consideration the populations, samples size, rare SNPs, functional study and gene-environmental interaction, the investigations will help us better understand the genetic basis of hypertension and blood pressure regulation, with potential benefits for prediction, early intervention, diagnosis and treatment.

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