

Genetics of hypertension: The lack of evidence

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Abstract

The silent killer or essential hypertension, is an important risk factor for cardiovascular disease, it affects 20% to 30% of the population worldwide and will alarmingly rise to 1.5 billion by 2020. Its heritability is around 31 to 68%, besides affecting environmental factors. Comparing to the last years, there have been a substantial progress in the understanding of the Blood pressure and HTN etiology. We provide an overview of the current findings of the GWAS aiming to contribute in the understanding of the pathophysiology of Blood pressure and HTN. From the fact that only a fraction of the phenotypic variability of BP can thus far be explained by the recently discovered common genetic polymorphisms from GWAS, therefore, we tried to highlight the major role of rare and structural variants, epigenetics in the missing heritability of HTN.

Key words: epigenetics, essential hypertension, heritability, GWAS.

Introduction

Hypertension is a chronic elevation of blood pressure, defined by systolic/diastolic blood pressure (SBP/DBP) above 140/90 mmHg. It affects 20% to 30% of the population worldwide and will alarmingly rise to 1.5 billion by 2025 [1]. Its importance as the most prevalent risk factor for the development of cardiovascular disease such as coronary artery disease and stroke has been consistently demonstrated across various population [2].

Hypertension is the result of the interaction between many risk genes with an estimated heritability ranging from 31% to 68%, and with

environmental factors such as: Dietary salt intake, alcohol consumption, smoking and ethnicity [3, 4]. Various family and twin studies have estimated the clinic heritability of systolic blood pressure and the diastolic blood pressure in the range of 15 to 40% and 15 to 30% respectively) [5, 6], whereas for ambulatory night-time systolic and diastolic blood pressure the heritabilities are 69% and 51% [7]. The sibling recurrent risk of hypertension is in the range of 1.2 to 1.5 [8], which indicate a phenotype with a modest genetic effect. Blood pressure is regulated by a complex network of interactive physiological pathways involving cardiac contractility and vascular tone through renal, neural or endocrine system, extracellular fluid volume homeostasis and any perturbation in these pathways can arise from genetic or environmental factors or both of them [9].

Fifty years ago after the Pickering-Platt's debate, little is known about the aetiology of such complex risk factor. In this review, we try to provide a general view of the major strategies done worldwide in these last year's aiming to understand the complexity of such important trait.

Genome-Wide Studies on Blood Pressure and Hypertension

Linkage studies

The linkage studies were the first genome-wide studies on human hypertension and blood pressure. They aim to find a physical linkage between a marker and a gene. These studies deal with family design, and refer to co-transmission of polymorphic genetic markers or traits linked on the same chromosome from parents to off-spring, using two well known statistical methods: Lod-score and affected sib-pairs

In 1995, the National Heart, Lung, and Blood Institute (NHLBI) have established a collaboration of 4 multicenter networks: GenNet (University of Michigan), GENOA (University of Texas at Houston), HyperGEN (University of Utah), and SAPPHiRe (Stanford) known as the "Family Blood Pressure Program (FBPP)". This collaboration aimed to investigate the genetic determinants of inter-individual blood pressure variation in Asians, African Americans, Mexican Americans, and Caucasians [10]. The FBPP collaboration yielded statistical power and unmatched diversity in any individual study [11]. The complete FBPP resource includes 13,516 individuals with microsatellite genotype data from two distinct temporally study phases (phase 1 and 2 were conducted from 1995-2000 and 2000-2005, respectively). The findings of this study were: five quantitative trait loci (QTLs) detected on chromosomes 6p22.3, 8q23.1, 20q13.12, 21q21.1, and 21q21.3 based on significant linkage evidence defined by logarithm of odds (LOD) score ≥ 3 in at least one meta-analysis and LOD scores ≥ 1 in at least 2 subgroups defined by network and race. The chromosome 8q23.1 locus was supported by Asian, Caucasian, and Mexican-American-specific meta-analyses [12].

Another important linkage study is the British Genetics of Hypertension (BRIGHT) study; where almost 2,010 affected sibling pairs from 1,599 severely hypertensive families were genotyped completing a 10cM genome-wide scan [8]. This study reported a principal locus on chromosome 6q with a lod score of 3.21 that reached genome wide significance ($P=0.042$). After assessment under locus-counting analysis, three loci have been identified on chromosome 2q, 5q and 9q with lod scores higher than 1.57, showing a genome-wide significance ($P=0.017$). However, this study presented some limitations such as insufficient sample size and marker density.

The availability of all these data, allowed a meta-analysis of 9 genome wide scans of blood pressure or HTN done by Koivukoski et al. [13] showing an evidence of susceptibility regions on chromosome 2 (2p12-q22.1) and 3 (3p14.1-q12.3). Many other genome wide linkage studies have been performed in different ethnicities revealing: No linkage with blood pressure while targeting chromosome 14 in Chinese population [14]. While, in European population, Mein et al. [15] have found a wide genome linkage on all chromosomes except 13, 20. Additionally, a 10 centimorgan genome-wide screen for systolic blood pressure (SBP) and diastolic blood pressure (DBP) performed in 1054 individuals from 188 rural Nigerian families population, has revealed many susceptibility locus on chromosome 6 and 7 [16].

On the other hand, linkage studied of non-European ancestry have reported a suggestive linkage detected for blood pressure on chromosome 2q and 22q in the population of Samoan islands [17]. There have been several recent linkage and association studies such as those performed by Guo et al. [18] using over 500,000 single nucleotide polymorphisms (SNPs) genotyped in 328 individuals from Chinese population, comprising 111 hypertensive probands and their siblings using a family-based association test, where they found an association with SNPs on chromosome 5q31.1 (rs6596140; $P < 9 \times 10^{-8}$) for hypertension where one candidate gene, *PDC*, was replicated, with rs3817586 on 1q31.1 attaining $P = 2.5 \times 10^{-4}$ and 2.9×10^{-5} in the within-family tests for DBP and MAP, respectively. They also identified regions of significant linkage for systolic and diastolic blood pressure on chromosomes 2q22 too and 5p13, respectively. Further family-based association analysis of the linkage peak on chromosome 5 yielded a significant association (rs1605685, $P < 7 \times 10^{-5}$) for DBP. It is the first combined linkage and association study of hypertension and its related quantitative traits with Chinese ancestry.

Despite all the advances in linkage studies, where

more than 30 genome wide linkage studies have been published on essential hypertension and blood pressure, but, it still presents some limitations such as: The need of great number of families, more knowledge on disease inheritance mode, penetrance and frequency fit much better with monogenic hypertension than essential hypertension.

Genome Wide Association Studies

Thanks to the modern genotyping techniques such as chip based genotyping arrays [19, 20] hundreds of thousands to more than one million SNPs of variants have been genotyped relying either on the knowledge of linkage disequilibrium (LD) available on (<http://hapmap.ncbi.nlm.nih.gov>) and the 1000 Genome project (<http://www.1000genomes.org>) which provide a catalog of human variants to help in the identification of disease-causing variants, or correlation patterns of imputed SNPs with functional variants, with fast and low cost.

Genome wide association studies (GWAS) or Hypothesis-free studies are based on the premise that a causal variant is located on a haplotype, and therefore a marker allele in (LD) with the causal variant should show by proxy an association with a trait of interest [21]. The approach is therefore said to be non-candidate-driven in contrast to gene-specific candidate-driven studies. There have been many reviews about the understanding of the GWAS [21, 22, 23].

In 2007, two large GWAS have been identified by Levy et al. [24] and the Wellcome Trust Consortium Case Control (WTCCC) [25], the former was based on Framingham heart study families with 100.000 polymorphic markers, using the Affymetrix 100Kchip, associating BP at two different time points and long term averaged BP. None genome wide significance was obtained, the latter was characterized by a better marker density, with 500.000

genetic markers using the Affymetrix (500Kchip), it was based on 2000 unrelated hypertensive subject from BRIGHT study [8] each for 7 complex diseases of major public health importance; bipolar disorder, coronary artery disease, Crohn's disease, hypertension, rheumatoid arthritis, type 1 diabetes, and type 2 diabetes. These were compared with 3000 shared common controls that came from two sources: 1500 from the 1958 British Birth Cohort and 1500 blood donors that were recruited for the project, over the entire genome there were 21 SNPs identified with P-values lower than the genome wide significance threshold of 5×10^{-7} . Unfortunately, from all the seven disease studied, no genome wide significance was obtained for hypertension, may be not due to the absence of association but to the study design which caused underperformance of HTN, or may be due to the undiagnosed of the controls, where it has reported that the misclassification of 5% of controls would translate to a loss of power equivalent to a 10% reduction in sample size [26].

To overcome these weaknesses, two important consortia were born, being more fruitful such as: The Global Blood Pressure Genetics (Global BPgen) consortium study, conducted by Newton-Cheh et al. [27] and the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) consortium study, conducted by Levy et al. [28]. The former tested 2.5 million imputed SNPs for association with SBP or diastolic BP in 34,433 subjects of European ancestry, there were eight loci associated with either DBP or SBP, with a genome wide significance, the variants were near CYP17A1, CYP1A2, FGF5, SH2B3, MTHFR, ZNF652, PLCD3 gene and chromosome 10 open reading frame 107 (c10orf107). It was also reported that these loci were associated with HTN, after a secondary analysis (N range = 57,410–99,802). The latter studied 2.5 million imputed SNPs for association in 29,136 subjects of European ancestry, a genome wide significance ($P < 4 \times 10^{-7}$) was achieved for 13 SNPs with SBP and 20 for DBP, 10

for hypertension [28].

To increase the power to detect association signals, a meta-analysis study [27] was performed including the two consortia (Global BP gen and CHARGE), the results showed a genome wide significance ($P < 5 \times 10^{-8}$) for CYP17A1, ATP2B1, PLEKH7, SH2B3, CACNB2, CSK-ULK3, TBX3-TBX5 and ULK4 for association with SBP or DBP or HTN. Despite this huge study, the effect sizes were very small, approximately 1mmHg change in SBP per allele or 0.5mmHg change in DBP per allele. Other important studies performed in 200,000 European individuals have developed a risk score from 29 genome wide significant variants where it has been associated with HTN and related target organ [29].

On the other hand, there were few published GWAS in individuals of non-European ancestry where we report some of them. A case control study of Han Chinese with 175 hypertensive cases and 175 normotensive controls using Affymetrix 100K, failed to identify genome-wide associated loci [30], followed by another Japanese GWAS Takushichi et al. [31] of 1,526 individuals including 403 cases and 452 controls, using Illumina Infinium HumanHap550 BeadArray, similarly did not reveal significant loci associated with HTN. However a meta-analysis of over 16,000 Korean individuals identified a BP-associated SNP (rs17249754, $P = 1 \times 10^{-7}$ in combined meta-analysis) near the ATP2B gene, the region also identified in the CHARGE Consortium [28, 32, 33]. These studies had limited statistical power due to study size and the restricted focus on HTN.

An important approach done in Japan called the Millennium projects which aimed to achieve bold technological innovation in three areas of vital importance to Japan: Information utilization, aging society and the environment. Among them, genome research in five fields of genetics, namely disease genes, human genome variation, the rice

genome, bioinformatics, and development/differentiation/regeneration. Two different approaches were launched, genome-wide association analysis using single-nucleotide polymorphisms (SNPs) and microsatellite markers, and systematic candidate gene analysis, under the hypothesis that common variants have an important role in the etiology of common diseases. These multilateral approaches identified ATP2B1 (gene which encodes the plasma membrane calcium ATPase isoform 1, which removes bicalcium ions from eukaryotic cells against very large concentration calcium homeostasis) as a gene responsible for hypertension in not only Japanese but also Caucasians [34].

From the other side of the globe, and despite the high prevalence of HTN in African Americans, there have been few published studies on BP, for example, one important GWAS in individuals of African ancestry included in the discovery sample of 509 hypertensives and 508 normotensive controls enrolled in Washington DC [16], in addition to another genetic association study performed by Fox et al. [35] in the same population, but both of them did not identify any genome-wide significant signals after the replication stages. Additional GWAS involving larger number of US minority participants are currently underway, including the Women's Health Initiative minority sample (WHI-SHARE) and the Candidate Gene Association Resource (CARE).

The findings from the GWAS, followed by the meta-analysis, have positively contributed to the understanding of a small part of the pathophysiology of HTN and BP, but didn't uncover yet the bottom of the iceberg.

Rare variants

Although, there have been a huge progress in the discovery of variants associated with the BP /HTN trait, the effect of these variants still too small with

a modest contribution on BP in the range of 0.5 to 1mmHg per allele. This may lead us to support the Platt's model, pointing out the major role of highly penetrant rare variants with large effect on BP trait [36]. Mendelian forms of Hypertension account only for 1% of human hypertension; however, they contribute to the understanding of the pathogenesis of hypertension. There have been many published studies about the Mendelian forms of hypertension, one of the important discoveries in these last years was the description of the mutations in the WNK1 (in the case of a gain function mutation) and WNK4 (loss function mutation) which are the cause of the Gordon syndrome (PseudohypoaldosteronismII) [37] this latter is an autosomic dominant form of HTN, characterized with hyperkalemia, an increase in salt absorption by the kidney, metabolic acidose. From different studies, it has been noticed that the variants of WNK1 gene are associated with blood pressure variation in a severely hypertensive [38] and in the general population [39].

In the contrast, mutations which cause reduce in salt retention are mainly associated with Bartter syndrome (SLC12A1, KCNJ1, CLCKB, BSND, CaSR, CLCK-A), and with Gitelman syndrome (SLC12A3). These latter are implicated in the lowering of BP and protecting against the development of HTN [37, 40]. The resequencing of these three genes in the Framingham Heart Study population (1.985 subjects and 1.140 relatives) has identified novel variation in these genes and defined the frequency of such variation in this population [40]. Thus, it has been identified 46 synonymous substitutions, 89 missense substitutions, one nonsense mutations and two frameshift mutations. These mutations appear to reduce the risk of hypertension by 60% at age of 60. In addition to these findings, one suggestive SNP (CASZ1, also replicated in a Japanese study) and one gene expression-associated SNP (BLK-GATA4 region) have reached genome-wide significance after meta-analysis combining the Women's Genome Health

Study with prior study results of CHARGE [41]. A novel locus for HTN (ZFATI), not tagged by SNPs, and replicated in an independent sample, has been identified by a recent Wellcome Trust Case Control Consortium (WTCCC) investigation [42]. However, the replication was not in the same block suggesting a role for multiple rare variants within the gene/region influencing the susceptibility to HTN. It is possible that a multitude of highly penetrant, low-frequency alleles affecting a variety of pathways involved in BP regulation explain a substantial proportion of the remaining heritability [43].

Novel pathway: UMOD gene's variant

The UMOD gene located on chromosome 16, encodes the Tamm-Horsfall protein (THP) or Uromodulin, most abundant protein in the urine, an extracellular protein anchored by a glycosyl phosphatidylinositol (GPI), produced by the thick ascending limb of the loop of Henle. According to Vyletal et al. [44], this protein plays a major role in the defense against urinary tract infections and in the formation of the kidney stones, particularly in autosomal dominant hyperuricemic nephropathy. It is also involved in progression of kidney disease and renal fibrosis [45, 46] serving as a marker in kidney disease [47]. In a large GWAS of extreme BP phenotypes and kidney function, where case and control subjects were recruited from the far needs of BP distribution in the general population it was reported that a variant in the 5' end of UMOD has been associated with HTN [48].

The Post GWAS

Structural variants

Common variants have been extensively characterized by GWAS but little is known about structural variations which refer to DNA segments that dif-

fer in copy number between individuals and they include insertions–deletions (indels), inversions, duplications, and other copy number variations (CNV) [49]. These kinds of variants are suspected to be involved in the missing heritability. The WTCCC study also investigated effects of common CNVs on eight complex diseases, including hypertension in Caucasians. The study replicated three loci where copy number variations were associated with various diseases, but not for the HTN trait. It has been noticed from this study that common CNVs tend to be well tagged by GWAS chips; therefore, it supposes that they don't contribute widely in the understanding of the pathophysiology of BP and HTN. Interestingly, Conrad et al. [50] recently showed that 474 of 1.521 polymorphic trait associated SNPs identified in GWAS of individuals of European ancestry fell within a recombination hotspot interval that also contained a copy number variation with correlations of 0.5 or higher. Knowledge of the involvement of indels in complex disease is limited, as no high-throughput detection technology is available. Examples of Alus exhibiting replicated association with BP are the classic polymorphic Alu-insertion (rs4646994: I/D) located in intron 16 of the ACE gene [51] and a recently discovered AluYb8 insertion in intron 10 of the WNK1 gene [52].

The role of the CNVs in other disease such as schizophrenia (SCZ) [53, 54] and autism [55, 56] myocardial infarction [57] has been promising.

Epigenetics

Not all gene regulation is encoded in the DNA sequence; BP genes can also be differentially regulated by epigenetic mechanisms, including methylation, histone modification, and miRNAs.

miRNAs

A small nucleotides (~22), regulatory, singlestranded RNA molecules, which function by reducing the expression of specific target genes, endogenous in origin and are transcribed as longer precursor RNA molecules that are processed into mature miRNAs capable of reducing the translation levels from the targeted mRNA and/or causing its degradation [58]. Currently, more than a thousand miRNAs have been identified in humans [59].

They participate in proliferation, differentiation, and cell death. Many models of tissue or cell-type specific dicerknockout mice have been created for vascular smooth muscle cells (VSMCs) [60], juxtaglomerular cells [61] and podocytes. The loss of miRNAs in juxtaglomerular cells and VSMCs causes significant reductions of BP. In case of juxtaglomerular cells, this difference can be attributed to reduced renin production [61] whereas in VSMCs the reduced BP is due to decreased vascular contractility, which can be attributed to a large extent (but not entirely) to the lack of miR-145 [60, 61]. For example, Mice lacking miR-143 and miR-145 develop significant reductions in BP resulting from modulation of actin dynamics [62].

In addition, an observational study showed that human cytomegalovirus (HCMV) seropositivity and titers are positively associated with essential hypertension independently of other HTN risk factors [63] and the infection of mice with mouse cytomegalovirus can alone elevate blood pressure [64] besides their role in maintaining vascular contractility, they can also control many components of the renin-angiotensinaldosterone system where it has been found in experimental study that mineralocorticoid receptor gene NR3C2 is downregulated by miRNAs miR-135a and miR-124 [65] added to several genes in the RAAS which are regulated by miRNAs [65, 66]. These findings point out the major role of the

miRNAs in regulating BP, but there is much more to uncover in the future, there have been many recent reviews focusing on this part [67, 68].

Histone modification

Another aspect of epigenetics is the histone modifications which are indicators of active or repressed chromatin, and the "histone code" hypothesis proposes that combinations of specific histone modifications define chromatin regulation and gene transcription [69, 70]. It has been found that modification in histone plays an important role in the epigenetic of epithelial sodium channel- α subunit (ENaC α) gene expression and modulation of WNK4 transcription in the development of salt sensitive HTN. For the former, Zhang et al. [71] have found that a nuclear repressor complex can regulate histone H3 Lys-79 methylation of chromatin associated with the ENaC α promoter and suppress its transcriptional activity.

For the latter, Mu et al. [72] have found in mice on a high salt diet showed that histone modification plays an important role in decreasing transcription of the WNK4 gene induced by β 2-adrenergic receptor stimulation where isoproterenol-induced transcriptional suppression of the WNK4 gene is mediated by histone acetylation in the promoter region of the WNK4 gene via inhibition of histone deacetylase-8 activity (HDAC8), which in turn can stimulate thiazide-sensitive Na⁺-Cl⁺ cotransporter (NCC/SLC12A3) providing that sympathetic nerve activity can increase BP partly by activating NCC [11].

DNA methylation

This process is intrinsically linked to the regulation of gene expression. Methylation changes of genes have recently been linked to a wide range of complex, often age-related diseases, including hypertension [73], diabetes [74], autoimmune disorders

[38], obesity [75], heart disease [76], and mental disorder [77]. More than 1.000 hypermethylated CpG sites were identified in the kidneys of salt-sensitive rats compared with normotensive Brown Norway rats, pyrosequencing of the promoter of renin genes showed that 10 CpG sites were significantly hypermethylated in salt-sensitive rats, consistent with the reduced renin expression in this strain. An example, Loss-of-function mutations of 11beta-hydroxysteroid dehydrogenase type 2 (11 β -HSD2) genes lead to a form of salt-sensitive monogenic hypertension [78]. Methylation modulation of this gene has recently been demonstrated in both a rodent model and cultured human cell lines [79]. A recent study [80] also showed increased methylation of several CpG promoter sites of HSD11B2 in kidneys from rat offspring suffering from intrauterine growth restriction.

The cis-regulation of DNA methylation by genetic variation may reflect the existence of a common pathway that acts on both genetic and environmental effects and represents a potential mechanism for gene-environment interaction.

Future Challenges

Although the recent advances in the GWAS including meta analysis of BP extremes, exome sequencing, The discovery of *KLHL3* as a cause of pseudohypoaldosteronism type II, [81] the increasing in the sample size of this latter which may lead to the identification of 116 common variants for BP that

have the same effect sizes as those identified already, but all this with a small contribution (2.2%) in the understanding of the BP heritability. In addition to the above-mentioned clues to understand or to uncover the pathophysiology of Hypertension and blood pressure, there is still some big challenges in finding answers to the missing heritability problem by a better focusing on epigenetic aspect, a better understanding of the gene-environment interaction (i.e: taking account the UMOD gene variant, some features of epigenetics and their relationship with environment), gene-gene interaction, accurate phenotyping (accurate BP measurement by ambulatory monitoring or home-measurement), a special focus on intermediate phenotype such as endothelial function, vascular stiffness besides associated phenotypes (body weight, renal function), translation findings from animals to man, a better focusing on rare and structural variants. When we will overcome all these challenges, then we can talk about translation of genetic findings into clinical practice.

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