Genomic Approaches to Hypertension

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KEYWORDS

• Hypertension • Blood pressure • Genomic approaches

KEY POINTS

- Genomic insights and analyses of Mendelian hypertension (HTN) syndromes and Genome-Wide Association study (GWAS) on essential HTN have contributed to the depth of understanding of the genetics origins of hypertension.
- Mendelian syndromes are important for the field, since such knowledge leads to specific insights about disease pathogenesis and the potential for precision medicine.
- The clinical impact of findings of GWAS on essential HTN is continuously evolving, and the accrued insights will refine efforts to combat the societal impact of hypertension.
- Comprehensive identification of all genomic variants of hypertension, along with their individual associated mechanisms, is paving the way forward in the era of personalized medicine.
- The overriding challenge for care providers is to reduce health inequities through improved compliance and, perhaps, new paradigms for implementation science that incorporates genomic medicine.

INTRODUCTION

Hypertension is the leading cause of cardiovascular morbidity and mortality worldwide,[1–3] affecting more than a third of the US adult population[4,5] with a disproportionate burden in underrepresented and ethnic minorities including African Americans.[6] In both personal and societal terms, blood pressure control has emerged as an important health indicator in the US population and for 1 billion people worldwide. To attain the American Heart Association Strategy Impact Goals to improve cardiovascular health of all Americans by 2020 and beyond, an ideal blood pressure target (<120/80 mm Hg) ranks among the 7 ideal health indicators[7] being directly targeted in populations. Although an in-depth review of the clinical manifestations, diagnostic evaluation, and treatment options of asymptomatic and symptomatic hypertension are covered elsewhere, this article reviews the genetic causes and provides a conceptual framework by which genomic analyses have propelled novel insights into the mechanisms of systemic and arterial hypertension.

Hypertension remains a significant public health problem with far-reaching impact on disease burden globally from stroke, heart failure, aortic dissection, atrial fibrillation, myocardial infarction, and end-stage kidney disease. In fact, a recent publication by Lawes and colleagues[8] concluded that 13.5% of premature deaths, 54% of strokes and 47% of ischemic heart disease worldwide are attributable to uncontrolled hypertension. Among the most easily recognizable and reversible risk factors, these authors further concluded that about 80% of the attributable burden

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occurred in low-income and middle-income economies. In spite of evidence of medical therapeutics and access to advanced systems of medical care, fewer than 50% of Americans treated for hypertension reach the target blood pressure goals. To achieve effective gains, both highly motivated and educated individuals affected with hypertension along with knowledgeable medical providers are prerequisites for proper blood pressure control and management.

Although the etiology of essential hypertension is unknown, both genetic and environmental factors play important roles in the pathophysiologic mechanisms in modern societies.[9] In epidemiologic studies among members of the Luo tribe in Kenya, for example, Poulter and colleagues[10] have highlighted lower blood pressure in their traditional rural environment compared with the urban center of Nairobi where urinary sodium and potassium concentrations was higher and lower, respectively. Because the renin-angiotensin- aldosterone system (RAS) has features for adaptation in sodium conservation, it has been hypothesized that a sodium-deprived environment favors sodium conservation as the default phenotype, underscoring the importance of salt reabsorption in the pathogenesis of hypertension in societies with high dietary salt intake.[11] In recent decades, substantial progress has been made to elucidate the mechanisms underlying the physiologic pathways and molecular targets of genes causally linked to rare Mendelian forms of hypertension in people.

GENOMIC VARIATION AND HUMAN INHERITABLE DISEASES

Thanks to the Human Genome Project, the promise to identify the consequence of germ line mutations (ie, single-nucleotide variants [SNV] and copy-number variants [CNV]) has yielded almost 3000 protein-coding genes linked to disease-associated mutations in people.[12] Innovations of genome sequencing coupled with technologies that dramatically reduce the amount of DNA required for coverage of coding regions have revolutionized the identification of rare variants and disease-causing mutations. Genomic approaches such as whole exome capture and sequencing technologies for increased sensitivity and specificity have provided an important means to investigate inheritability factors of hypertension. Indeed, proof of concept for whole-exome sequencing has been validated as a clinical diagnostic tool for the evaluation of patients with previously undiagnosed genetic disease.[13]

For Mendelian diseases, the discovery of the genetic basis is central to establishing causality between genotype and phenotype and the foundation for genetic screening and diagnosis in affected populations. Studies from family and twin research suggest that blood pressure is moderately heritable (30%–50%).[14] However, the extent to which the percentage of inheritability influences the development of hypertension has been previously challenged.[15] When single-gene mutations result in the large effects on the phenotype, then applications of next-generation sequencing have identified rare variants with moderate-to-large effects, especially in populations of phenotypic extremes.

Along with traditional cardiovascular risks factors, 2 broad groups of genomic variants have been proposed to influence the development of hypertension. These are the effects of genomic variants on the development of rare familial syndromes that lead to monogenic hypertension (HTN) and the genetic variants underlying common essential HTN. These rare familial genome variants with monogenic hypertension have large effects, potentially triggering hypertensive crises with severe cardiovascular morbidity and mortality. However, the many genetic variants with small effects likely underlie the polygenic trait of common essential HTN in people. Thus, familial hypertensive syndromes are rarely caused by monogenetic variants that significantly influence an increase in blood pressure with variable effect size. In these hypertensive syndromes, patients develop HTN at an early age (**Table 1**) and have effect sizes as much as 10 mm Hg in systolic blood pressure.

THE GENOMIC VARIANTS IN BLOOD PRESSURE REGULATION CAUSING RARE FAMILIAL HYPERTENSIVE SYNDROMES

Because large fractions of interindividual variability can be attributed to genetic determinants, the pursuit of rare disease-causing mutations using genetic approaches has successfully yielded substantial insights into the pathophysiology of hypertension while simultaneously affording new opportunities for tailored therapies in the era of precision medicine. Several monogenic variants have established Mendelian modes of inheritance.[33,34] Twelve genes have been identified, modulating and influencing the development of 8 distinct rare familial hypertensive syndromes, all of which are inherited in a Mendelian fashion. **Table 1** summarizes these genetic variants including key features of each clinical syndrome. Recently, 2 of the 4 genes known to cause Gordon syndrome were identified.[22,24] Other Mendelian HTN syndromes have been mapped to genomic regions,