Curr Cardiovasc Risk Rep (2015) 9: 1
DOI 10.1007/s12170-014-0429-y

HYPERTENSION (R TOWNSEND, SECTION EDITOR)

Genetics of Hypertension: What Is Next?

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Published online: 27 January 2015

Abstract Hypertension or an elevated blood pressure continues to be a major risk factor for cardiovascular disease. Despite intensive public education including lifestyle modification programs and the availability of safe and effective pharmacologic agents to treat hypertension, the treatment and control of hypertension is suboptimal. Over the past several decades, there have been tremendous advances in the use of genetics to prevent, detect, and treat human disease states. Despite these advances and an intensive effort, the application of genetics to the broad population with hypertension has not met expectations. This review will address our present understanding and use of genetics in hypertension and areas where genetics may impact significantly our approach and clinical treatment of hypertension in the future.

Keywords Hypertension · Genetics · Epigenetics · Methylation · Histone, candidate genes · Liddle's syndrome · Aldosterone · Renin · Angiotensin · Acetylation

Introduction

Despite the recognition that hypertension significantly increases the risk for cardiovascular disease, congestive heart failure, and stroke, it continues to remain a major public health issue affecting approximately one billion individuals globally and 50 million individuals in the USA. Given the increase in life expectancy and the marked increase in obesity and diabetes, the prevalence of hypertension is likely to increase even further. Unfortunately, data (2009–2010) from the most recent report of the National Health and Nutrition and Examination Survey (NHANES) conducted in the USA showed that although approximately 80 % of Americans know that they have hypertension, less than half of these individuals have their blood pressure controlled to less than 140/90 mmHg [1, 2].

One of the major advances in the field of medicine over the last few decades has been the increased recognition of the importance of the genetic basis of disease coupled with the interaction with environmental factors, as well as the discovery, development, and clinical use of powerful genetic technologic tools. These discoveries have impacted significantly several disease states, most notably cancer. Interestingly, while a great deal of research and scientific expertise has been devoted to understanding the genetic basis of hypertension with the potential to have a significant impact on its detection and treatment, progress has largely lagged behind expectations. Several explanations have attempted to explain this observation, the most notable of which, that unlike other disease states, hypertension, particularly "primary" or "essential" hypertension, is heterogeneous and occurs across a wide range of demographics and populations. This review will address what is known presently and the clinical application regarding the genetics of hypertension but more importantly, where the field may be going in the future. It will explore various areas of genetics such as the role of monogenetic and complex disease states, candidate genes, epigenetics, the assimilation of large genetic data banks or sets, and finally, the potential for genetics to play a key role in the personalized treatment of hypertension.

This article is part of the Topical Collection on *Hypertension*

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Historical Perspective

The history of the genetic basis of hypertension parallels that of other common adult-onset complex traits. Beginning with the discovery of the first DNA sequence polymorphisms in 1979, there has been a concerted effort to uncover the genetic mechanisms underlying complex human disorders, including hypertension. The Human Genome Project generated a complete genetic map of the human genome including the genes responsible for many inherited diseases. These discoveries became crucial to the expansion of the field of medical genetics, helping drive the investigation into disease-causing genes.

While the refinement of genetic mapping was crucial for localizing a large number of Mendelian disorders, classical linkage analysis has significant limitations when applied to complex traits and disorders. Most importantly, its use is essentially confined to genes that act in a deterministic manner to produce some overt phenotype. Prior to the completion of the Human Genome Project in 2003, it was difficult to use candidate gene analyses for disorders with complex inheritance patterns. While some monogenetic causes of hypertension are known, they remain relatively rare, accounting for only about 1 % of the patient population with hypertension. We remain unable to explain the pathophysiologic basis of the majority of patients with hypertension. As the human genome project came to completion, it was clear that new approaches would also need to be developed to unravel the roles of genes in the etiology of primary or essential hypertension.

The discovery of single nucleotide polymorphisms (SNPs) and other DNA sequence variants that are widely prevalent and dispersed throughout the genome led to new approaches aimed at unraveling the role of genes associated with a wide array of common adult-onset disorders with complex inheritance patterns. However, despite significant advancements in genetic analysis methodologies, two major limitations to large-scale DNA sequencing remained: the high cost of DNA sequencing and the slow laborious nature of sequencing methods. More recently, however, next-generation sequencing (NGS) was developed which enabled the sequencing of 30–60 million reads per run. Next-generation sequencing now represents a variety of newly developed methods of DNA sequencing, including pyrosequencing, sequencing by synthesis, and pH-based sequencing, among others. These have increased significantly the efficiency of sequencing methods while lowering the cost of DNA sequencing. With DNA sequencing now relatively affordable and the results timely, there has been an exponential growth in the field. Unlike monogenetic causes of hypertension, where a mutation in an individual gene causes the phenotype, it is now apparent that individual SNPs contribute only a small degree to the overall phenotype of a disease. However, the cumulative effect of several SNPs could possibly explain a larger amount of the phenotype, including the development and presence of hypertension.

Genome-wide association studies (GWAS) could also contribute to our understanding of hypertension. These studies evaluate differences in allele frequencies between controls and patients diagnosed with a specific disease. This approach relies upon the existence of pervasive linkage disequilibrium within the human genome so that nearly every disease-causing gene has a nearby genetic marker that is easily detectable and can function as a surrogate marker for the gene itself. When a statistically significant association is determined for a specific marker in patients with a disease (such as hypertension) [3], the region surrounding the marker is searched for a gene (or genes) that may be responsible for or associated with the disease phenotype. Starting with the first GWAS published in 2007, the development of this technology has increased dramatically the rate of discovery of disease-associated SNPs. The NIH Catalog of Published Genome-Wide Association Studies lists nearly 2000 completed GWA studies, including 14 studies of hypertension. However, the clinical utility and application of GWAS is often limited, in large part, due to low statistical power. Furthermore, due to the isolated nature of much of the work, the vast majority of data has been compiled from small studies and geographically from Western populations, and thus, may not reflect variations in race, ethnicity, geography, and socioeconomic status.

Monogenetic Hypertension

Due to the important role of electrolytes, particularly sodium, in the pathogenesis of hypertension, research has long centered on the role of genes involved in sodium and fluid balance in the hypertensive process. In addition, due to the interaction of sodium and the renin-angiotensin-aldosterone system, several of the Mendelian genes involved in hypertension also influence the activity of the renin-angiotensin-aldosterone system. To date, many such genes have been identified, leading to at least eight distinguishable syndromes which are directly associated with blood pressure regulation, including hypertension. The study of these genes has unlocked the mechanism(s) behind a cluster of diseases termed monogenetic hypertension. Traditionally thought to be inherited in an autosomal dominant fashion, as with Gordon syndrome and Liddle syndrome, some autosomally recessive hypertensive syndromes have also been discovered. Together, these diseases are discussed below (Tables 1 and 2). While these diseases account for less than 1 % of all human hypertension, they provide clues to the intricate regulation and control of blood pressure. While additional monogenic causes of hypertension almost certainly will be discovered, the investigation of monogenic genes may also lead to new gene clusters that

Table 1 Glossary of genes

Gene	Full name	Product
SCNN1A	Sodium channel, nonvoltage-gated 1 alpha	ENaC subunit alpha
SCNN1B	Sodium channel, nonvoltage-gated 1 beta	ENaC subunit beta
SCNN1G	Sodium channel, nonvoltage-gated 1 gamma	ENaC subunit gamma
WNK1	With no lysine (K) kinase 1	
WNK4	With no lysine (K) kinase 1	
AGT	Angiotensinogen	
ACE	Angiotensin-1 converting enzyme	
AT1	Angiotensin-1 receptor	
ADD1	Adducin 1	Alpha-adducin
ATP1B1	Beta subunit of Na/K ATPase	
CYP3A5	Cytochrome P450 3A5	
NOS2A	Nitric oxide synthetase 2A	
NOS3	Nitric oxide synthetase 3	
GNB3	G-protein beta 3 subunit	
RGS5	Regulator of G-protein signaling 5	
HYT1-6	Hypertension genes 1-6	
NEDD4L	E3 ubiquitin-protein ligase NEDD4-like	Nedd4-2
SGK1	Serum/glucocorticoid regulated kinase 1	
Usp2-45	Ubiquitin specific peptidase 2	
SLC12A3	Solute carrier family 12, member 3	NCCT
SLC12A2	Solute carrier family 12, member 2	NKCC2
STK39	Serine threonine kinase 39	SPAK
KCNJ1	Potassium inwardly-rectifying channel, subfamily J, member 1	ROMK1
ACE2	Angiotensin-converting enzyme 2	
AQP4	Aquaporin 4	
NPPA	Natriuretic peptide A	ANP
NPPB	Natriuretic peptide B	BNP
Cx40	Connexin 40	
Cx43	Connexin 43	

are involved in the polygenetic nature of the remaining individuals with hypertension.

The autosomal dominant Liddle syndrome is a classic example of a monogenetic syndrome associated with hypoaldosteronism. Liddle syndrome is the most common monogenetic form of hypertension, characterized by the triad of hypertension, hypokalemia, and metabolic alkalosis. Liddle syndrome is the result of mutations in the genes which encode the β and γ subunits of the epithelial sodium channel (ENaC), the dominant sodium channel in the aldosterone-sensitive distal nephron (ASDN) in the kidney. These subunits are needed for the optimal expression and degradation of ENaC. Mutations in these subunits result in ineffectual suppression of the ENaC, which leads to the persistent expression of the channel at the cell surface in the aldosterone-sensitive distal nephron. Sustained activation of ENaC results in excess sodium reabsorption, leading to water retention and ultimately elevated blood pressure. The excess sodium feeds back on the renin-angiotensin-aldosterone system, decreasing renin and resulting in undetectable aldosterone levels. In addition to Liddle syndrome, both congenital adrenal hyperplasia types IV and V lead to the development of hypertension and are associated with decreased aldosterone.

In contrast, Gordon syndrome, also called pseudohypoaldosteronism type II or familial hyperkalemia hypertension syndrome, was initially thought to be associated with hypoaldosteronism. The term "pseudohypoaldosteronism" has historically been used to describe the finding of persistent hyperkalemia, despite the presence of normal or elevated serum levels of aldosterone [4]. The term was initially used to describe persons with an inherited disorder characterized by hyperkalemia, elevated serum aldosterone, and volume depletion (now referred to as pseudohypoaldosteronism type I). Gordon syndrome is a predominantly autosomal dominant disorder, with rare autosomal recessive families, which results from mutations in the genes coding serine/threonine kinases (WNK1 and WNK4) which regulate ENaC. Aldosterone levels are variable

Table 2 Autosomal recessive and dominant blood pressure syndromes

Syndrome	Gene	Mode of inheritance	Blood pressure	Serum aldosterone	Serum renin	Serum K+	Urine pH	Clinical implications
Autosomal recessive blood pressure syndromes								
Bartter syndrome	*SLC12A1* (type 1)	AR	Low	High	High	Low	High	Increased salt intake
	KCNJ1 (type 2)	AR	Low	High	High	Low	High	Increased salt intake
	CLCNKB (type 3)	AR	Low	High	High	Low	High	Increased salt intake
	BSND (type 4)	AR	Low	High	High	Low	High	Increased salt intake
Gitelman's syndrome	*SLC12A3* (NCCT)	AR	Low	High	High	Low	High	Increased salt intake
SeSAME/EAST	*KCNJ10*	AR	Low	High	High	Low	High	Increased salt intake
Renal tubular dysgenesis	*REN*	AR	Low	Low	Low/high	High	Low	Vasopressors
	AGT							
	ACE							
	AGT1							
Apparent mineralocorticoid excess	*HSD11B2*	AR	High	Inappropriately low	Low	Low	High	Aldosterone receptor antagonist (spironolactone) and/or ENaC blocker (amiloride)
Congenital adrenal hyperplasia	*CYP17A1*	AR	High	Inappropriately low	Low	Low	High	Aldosterone receptor antagonist (spironolactone) and/or ENaC blocker (amiloride)
	CYP11B1	AR	High	Inappropriately low	Low	Low	High	Aldosterone receptor antagonist (spironolactone) and/or ENaC blocker (amiloride)
Autosomal dominant blood pressure syndromes								
Glucocorticoid remediable aldosteronism	*CYP11B1/CYP11B2*	AD	High	Inappropriately high	Low	Low	High	Aldosterone receptor antagonist (spironolactone) and/or ENaC blocker (amiloride)
Aldosterone producing adrenal adenomas	*KCNJ5*	AD/denovo	High	Inappropriately high	Low	Low	High	Aldosterone receptor antagonist (spironolactone) and/or ENaC blocker (amiloride)
Liddle's syndrome	*SCCN1B*	AD	High	Inappropriately low	Low	Low	High	ENaC blocker (amiloride)
	SCCN1G	AD	High	Inappropriately low	Low	Low	High	ENaC blocker (amiloride)
Pseudohypoaldosteronism type 1	*NR3C2* (type 1A)	AD	Low	High	High	High	Low	Increased salt intake
	SCCN1A (type 1B)							
	SCCN1B (type 1B)							
	SCCN1C (type 1B)							
Gordon's syndrome (Pseudohypoaldosteronism II)	*WNK1*	AD	High	Inappropriately high	Low	High	Low	Thiazide diuretic
	WNK4	AD	High	Inappropriately high	Low	High	Low	Thiazide diuretic

Table 2 (continued)

Syndrome	Gene	Mode of inheritance	Blood pressure	Serum aldosterone	Serum renin	Serum K+	Urine pH	Clinical implications
	CUL3	AD	High	Inappropriately high	Low	High	Low	Thiazide diuretic
	KLHL3	AD	High	Inappropriately high	Low	High	Low	Thiazide diuretic
Hypertension of pregnancy	*NR3C2*	AD	High	Inappropriately low	Low	Low	High	ENaC blocker (amiloride)
Bartter syndrome	*CASR* (type 5)	AD	Low	High	High	Low	High	Increased salt intake

in this group of patients, and tend towards lower levels, on average and often present with a mild metabolic acidosis.

In addition, glucocorticoid remediable hyperaldosteronism also leads to the development of hypertension and is the result of a duplication of the gene encoding the 11β-hydroxylase enzyme. In this monogenic syndrome, ACTH stimulates aldosterone production, independent of renin. The resulting high levels of aldosterone stimulate the renal mineralocorticoid receptor which increases renal sodium reabsorption and urinary potassium excretion.

For any autosomal dominant hypertension syndrome, it is important to test first-degree relatives in order to diagnose and treat family members at the earliest possible age. The recurrence risks are 50 % for offspring of an affected individual. For recessive monogenic forms of hypertension, there is a 25 % recurrence risk among siblings, with relatively little risk to other family members.

Polygenetic Causes of Hypertension

Through a series of GWA studies, multiple genes have been found to be associated with the development of essential hypertension. To date, there have been greater than 20 genes thought to play significant roles in blood pressure regulation. Although multiple classifications can be proposed, one classification is to divide these genes into categories such as genes involving the following: (1) sodium/water homeostasis (e.g., ENaC, WNK1, and WNK4), (2) the renin-angiotensin-aldosterone system (e.g., AGT, ACE, and ATR1), and (3) vasoactive biomolecules (e.g., α-adducin (ADD1) and the natriuretic peptides). It is important to acknowledge that even this classification is arbitrary and there is overlap among genes and categories. For example, ADD1 is also involved in water and sodium balance. While not a complete list, these represent the vast majority of the work in this area.

In each of the abovementioned classes, there have been recent additions. These include the following: sodium-potassium ATPase subunit beta 1 (ATP1B1) and cytochrome P450, family 3 and subfamily A, polypeptide (CYP3A5) which involve sodium/water homeostasis; endothelin converting enzyme 1 (ECE1) and nitric oxide synthetase 2A and 3 (NOS2A, NOS3) which are vasoactive biomolecules; as well as G-protein beta polypeptide 3 (GNB3) and regulator of G-protein signaling 5 (RGS5) which could be categorized as G-coupled biomolecules that are involved in cell signaling pathways. Furthermore, recently, a new group of genes have been described, known as the HYT gene series (HYT1-6). While their locations have been revealed, their function remains elusive. Due to the limitations of this review, these will not be discussed in detail.

Genes Involving Sodium/Water Homeostasis

The ENaC belongs to the degenerin family of ion channels and represents a dominant mechanism of sodium reabsorption by the kidney. ENaC mediates the rate-limiting step in sodium transport and is crucial for sodium homeostasis. ENaC is localized in the apical membrane of epithelial cells throughout the body including the lung, exocrine glands, colon, and crucially, the aldosterone-sensitive distal nephron (ASDN). The structure of ENaC is well documented and consists of three subunits: α, β, and γ [5]. Mutations in the β and γ subunits cause both hypertension (Liddle syndrome) and hypotension (Gordon syndrome or pseudohypoaldosteronism type II). While the β and γ subunits modulate its peak activity, ENaC expression is tightly controlled by both aldosterone and vasopressin [5, 6]. Recent work has demonstrated additional control mechanisms of ENaC expression, which include the role of WNK1 (with no k-lysine kinase) as well as Nedd4-2, a specific ubiquitin ligase [5, 7]. WNK1 has been shown to activate ENaC, while Nedd4-2 serves to ubiquinate ENaC, which then promotes internalization and degradation [5, 7, 8••, 9, 10]. Given that Nedd4-2 binds to the β and γ subunits of ENaC, mutations to those subunits impairs the ability of Nedd4-2 to facilitate degradation of ENaC [7, 8••, 9]. This results in the accumulation of active ENaC channels at the cell surface which increases renal sodium retention [7, 11]. Given the intricate relationship of these components in sodium regulation, it is logical that they represent potential genetic targets that may be involved in blood pressure regulation and, ultimately, hypertension.

Aldosterone also has an intricate relationship with ENaC. Aldosterone induces serum and glucocorticoid-regulated kinase 1 (SGK1), which elevates in turn increases ENaC expression and activity at the cell surface [5, 7]. This is achieved through two separate mechanisms. In one mechanism, SGK1 phosphorylates Nedd4-2, disrupting the ubiquitylation of ENaC subunits, and reducing ENaC targeting for degradation [5]. In another mechanism, aldosterone, through SGK1, upregulates the activity of the deubiquitylating enzyme Usp2-45 which increases further full ENaC expression at the cell surface [9]. Studies of Nedd4-2 have revealed that single nucleotide polymorphisms of Nedd4-2 result in a nonfunctional Nedd4-2 and reduced ubiquitination of ENaC [7, 8••, 9]. Gain of function mutations in SGK-1 may be involved in salt sensitivity (an increase in blood pressure following increased sodium intake) as well as play a role in enhancing the power of genomic risk scores.

It has long been recognized that salt homeostasis can be altered with the use of thiazide-type diuretics by blocking the NaCl co-transporter, NCCT. While the vast majority (60–70 %) of filtered sodium is reabsorbed in the proximal tubule, 20–30 % is reabsorbed by the Na/K/2Cl co-transporter, NKCC2, and the final 5–7 % is absorbed by the thiazide-sensitive NCCT in the distal convoluted tubule [6]. However, the regulation of NCCT was not clearly understood prior to the discovery of Gordon's syndrome (pseudohypoaldosteronism type II). It was discovered that NCCT activity is modulated by both WNK kinases as well as a signaling cascade known as SPAK. The WNK gene encodes cytoplasmic serine-threonine kinases with WNK1 expressed in the distal nephron. Genetic manipulation of the NCCT has demonstrated changes in blood pressure in the predicted direction. Loss of function mutations of NCCT leads to salt wasting and hypotension, as seen in Gitelman syndrome. Loss of function mutations in WNK, which controls NCCT cycling and degradation, results in decreased NCCT degradation [6]. WNKs affect blood pressure, in part, by a failure of WNK to divert NCCT for degradation, causing increased sodium reabsorption through the transporter.

In addition to altering NCCT activity, WNKs also modulate other mechanisms involved in sodium homeostasis. WNK1 serves a dual purpose by inhibiting WNK4 and activating ENaC [6, 12•, 13•, 14]. While genetic studies of WNK have been limited, some promising results have been published. Specifically, deletions of the first intron of WNK1 have been linked to Gordon syndrome [13•, 14, 15]. Loss of function mutations in WNK1 causes the unique presentation of hypertension with hyperkalemia [14]. Given the central nature of the interrelationship of WNK with ENaC as well as NCCT, it seems to be a fertile area for future genetic research in hypertension.

Activity of NCCT is also affected by SPAK [6]. SPAK is a serine/threonine kinase encoded by the gene STK39. It functions to phosphorylate a variety of cation-chloride co-transporters, including NCCT. Furthermore, SPAK-deficient mice exhibit a Gitelman syndrome-like phenotype [6]. Given the dramatic effects of the NCCT/SPAK/WNK pathway on blood pressure regulation, it is theorized that SPAK selective inhibitors may prove to be highly effective thiazide-like diuretics, and thus a new pharmacologic target for the treatment of hypertension. This is highly promising as a SPAK inhibitor may display thiazide-like effectiveness without any of the common metabolic side effects such as hyperglycemia and hyperuricemia [6].

Discovered through a Framingham Heart Study GWAS, the KCNJ1 gene helps encode an ATP-dependent potassium channel called renal outer medullary potassium channel (ROMK1), which modulates the resorption of potassium in the thick ascending limb and collecting duct of the nephron. Furthermore, ROMK1 may modulate the activity of the NKCC2, a sodium channel responsible for reabsorption of sodium in the thick ascending portion of the loop of Henle [14]. Loss of function mutations in KCNJ1 results in a nonfunctional ROMK1. This prevents NKCC2 from reabsorbing sodium, resulting in reductions in blood pressure. Additionally, WNK1, as well as WNK4, stimulates endocytosis of

ROMK1. This pathway has only recently been described and may be found in patients with primary hyperaldosteronism. Despite limited understanding of KCNJ1 and ROMK, they may prove to be lucrative research targets for both genetic and pharmacologic investigation in hypertension, such as the development of a new class of diuretic agents which promote diuresis without hypokalemia, as is seen with the use of thiazide and loop diuretics [14]. While the majority of the work has revolved around the study of ENaC as well as the various WNKs, substantial work has been done in the study of the subunits of the Na+/K + ATP pump, specifically ATP1b1 as well as the cytochrome P450, CYP3A5.

Genetics Involving the Renin-Angiotensin-Aldosterone System

Due to its important role in blood pressure and sodium regulation, the association between the renin-angiotensin-aldosterone system (RAAS) and hypertension has been intensely studied. Genetic targets of the RAAS include angiotensinogen (AGT), angiotensin-converting enzyme (ACE also termed ACE1), angiotensin-converting enzyme 2 (ACE2), and the angiotensin-1 (AT1) receptor. Since angiotensinogen, generated in the liver, initiates the cascade of the RAAS, it was an early target for genetic research. Studies have demonstrated that genetic polymorphisms of AGT, particularly of the promoter region of AGT, lead to the increased expression of AGT, which increases angiotensin II levels. Furthermore, studies have investigated the possibility that there may be gender-specific mutations in the AGT gene. For instance, the presence of a mutation, M235T, has been found primarily in women [16]. This mutation appears to have a linear correlation with the development of hypertension in Southeast Asian women. In addition, individuals who are homozygous for the M235T mutation may exhibit increased activity of the RAAS and a greater blood pressure-lowering effect of angiotensin-converting enzyme inhibition. It is thought that polymorphisms in AGT alter salt sensitivity by enhancing nerve activity, raising risk of ischemic heart disease and hypertension [17]. While its clinical importance remains unclear, the M235T mutation may prove to be a marker for an increase in blood pressure and an enhanced blood pressure-lowering effect of pharmacologic RAAS inhibition.

Angiotensin II (AngII), the primary active component of the RAAS, results when the ACE gene encodes angiotensin-converting enzyme which converts angiotensin I to angiotensin II. While the intense initial research in ACE culminated in the development of ACE inhibitors, it remains unclear how much genetic variability in ACE contributes to the development of hypertension. ACE has gene polymorphisms that either insert (I) or delete (D) 287 bps in intron 16 of the ACE gene. This results in the homozygotes I/I and D/D and the heterozygote I/D. The I/D heterozygote polymorphism may account for as much as 50 % of the interindividual variation of ACE activity. ACE levels correlate with the presence of the D allele, with lower levels of ACE activity in the I/I, moderate levels in the I/D, and highest levels in the D/D genotype [8••, 18–21]. Preliminary data has found that presence of the I/D polymorphism may be an important factor in predicting the response to HCTZ [22]. D/D homozygotes also have an increased risk of developing hypertensive urgency and hypertensive crisis [23]. While it has been theorized that ACE levels increase the risk of hypertension, this concept continues to be controversial [22, 24]. Future work would require higher powered studies through larger sample sizes in order to elucidate further the clinical utility of genetic variants of ACE in populations and/or individuals with hypertension [18]. However, given the importance of ACE as the rate-limiting step of angiotensin II generation, future research in this area seems warranted.

Initially discovered in 2000, ACE2 has become an important target for research involving the RAAS. ACE2 is the first human homologue of ACE and is distributed widely throughout the body. It is mainly expressed in cardiac blood vessels and the tubular epithelia of the kidneys. It degrades both angiotensin I and angiotensin II. Thus, increased activity of ACE2 could lead to a reduction of blood pressure by decreasing the activity of the vasoconstrictor angiotensin II. For instance, ACE2 knockout mice exhibit a 10-mmHg higher blood pressure, which is consistent with a hypotensive effect of ACE2 activity [25]. In addition to decreasing angiotensin II levels, ACE2 converts angiotensin II to angiotensin 1-7, a vasodilator, which could also lower blood pressure [25]. The two major arms of blood pressure control—ACE/AngII/angiotensin 1 receptor (vasoconstrictor) and ACE2/Ang1-7/angiotensin 1-7 receptor (vasodilator)—balance one another [26]. Analysis of the ACE2 gene, using SNPs, has demonstrated that the promoter sequence of ACE2 is highly polymorphic [25]. This raises speculation that structural or expression variation in ACE2, leading to loss of function, may result in hypertension and/or tissue damage, while changes that result in gain of function may lead to lower blood pressure and/or tissue protection. Interestingly, ACE2 levels are elevated in patients with advanced coronary artery disease and heart failure, which may be a manifestation of the cardioprotective function of ACE2 [26]. Thus, ACE2 remains an interesting target for future research regarding the genetic basis of hypertension.

Angiotensin II is the primary active end product of the RAAS. Among many other functions, AngII causes vasoconstriction and stimulates aldosterone secretion. This response is initiated by AngII binding to the G protein coupled receptor (GPCR), known as AT1. Given its importance in the development of hypertension and cardiovascular disease, like ACE,

significant research has been directed to AngII. This work has resulted in the development of the pharmacologic class of angiotensin receptor blockers. While much of the work has been in the study and synthesis of AngII receptor binding compounds, little is known about the role of clinically significant genetic mutations of the AngII receptor that lead to changes in receptor activity and thus blood pressure.

Genes Involving Vasoactive Peptides

Adducins (ADD) are a class of cytoskeletal proteins that regulate the membrane organization of spectrin-actin. They are thought to be instrumental in the development of salt sensitivity of blood pressure. Mutations in ADD1 have long been shown to induce vascular remodeling. They have also been shown to increase the expression of the Na/K-ATPase resulting in abnormal renal sodium transport in humans by limiting the endocytosis of the pumps. Additionally, mutations in ADD1 also affect the expression of aquaporins, specifically AQP4 which is constitutively expressed only in the collecting duct [16, 27]. AQP4 expression causes increased water absorption in the collecting duct, which drives the need for increased Na/K-ATPase expression [16]. It has been theorized that given the basolateral expression of both Na/K-ATPase and AQP4, ADD1 mutations primarily affect the rate of AQP4 endocytosis, which alters the regulation of Na/K-ATPase [27, 28]. There is potential that a new class of AQP4 inhibitors could be developed as pharmacologic antihypertensives. Genetic mutations in ADD1 may then serve as a predictor of antihypertensive efficacy of AQP4 inhibitors.

Genes Potentially Involved in Human Hypertension

Natriuretic peptides are a family of molecules that include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). ANP and BNP are synthesized primarily in the heart, while CNP is produced by endothelial cells. The natriuretic peptides are encoded by natriuretic peptide A (NPPA) and natriuretic peptide B (NPPB) [29, 30]. In target tissues, soluble guanylyl cyclase receptors (GC) modulate the biologic effects of the natriuretic peptides by increasing cGMP following binding of ANP/BNP to NPR-A and by decreasing cGMP levels following the binding of CNP to NPR-B [30]. Activation of the NPR-A receptors lowers blood pressure. The mechanism of this hypotensive activity is by promoting vasodilation by inhibiting the contraction of vascular smooth muscle cells through cGMP-dependent kinases [30]. GWAS performed in both Caucasian and Asian populations have found genetic variants acting at the MTHFR-NPPB locus, which may raise ANP and BNP levels and lower blood pressure [9]. Additionally, coding variants in the NPPA gene have been linked to endothelial-dependent impaired vasodilatation, without grossly affecting blood pressure. Further work in these patients has found that the resultant ANP varies structurally and preferentially activates NPR-C, causing endothelial dysfunction. As a result, in patients carrying this mutation, selective blockade of the NPR-C may provide a novel method of reducing overall cardiovascular risk [30]. Other studies have found that deletions in the NPPB gene have been associated with development of salt-sensitive hypertension in mice [14]. Human studies have thus far failed to show clinical utility at this point, but the work remains ongoing.

Since nesiritide, a recombinant form of human BNP, has been shown to lower blood pressure when administered in high dose in humans, specific targeting of these receptors has been an attractive target for future therapy. There has been substantial work in an attempt to produce a functional ANP homologue as an antihypertensive medication. While the infusion of ANP has been proven to reduce BP and cause natriuresis and diuresis, peptide stability has limited the development of oral agents [30]. While still in clinical development, a novel class of drugs which combine angiotensin II receptor blockade and neutral endopeptidase inhibition has been developed that lowers blood pressure to have greater extent than angiotensin II blockade alone [30]. It remains to be determined whether genetic variations in this system will have clinical applicability.

As early as 2001, the Connexin (Cx) 40 protein has been linked with the development of hypertension in mouse models. Cx40 is a protein expressed in both endothelial cells and in renin-producing cells. Along with Cx37, Cx43, and Cx45, Cx40 helps comprise the gap junctions used by juxtaglomerular cells to connect to each other and to endothelial cells of afferent arterioles. Early work found that Cx40-deficient mice develop hypertension [31, 32]. These mice also exhibit aberrations in the distribution of renin-producing cells in the kidney, often with cells found ectopically outside the arteriolar vessel wall [31]. Therefore, any renin secreted by these cells could be independent of normal feedback mechanisms [31]. Additionally, it has been demonstrated that deletion of the Cx40 gene in renin-producing cells with Cx40 intact in epithelial cells results in hypertension. In contrast, deletions of Cx40 in epithelial cells with Cx40 intact in renin-producing cells have normal levels of renin and no change in blood pressure [32]. More recently, Cx43 has been shown to be upregulated in renin-dependent hypertension [33]. While interesting, the clinical significance of Cx40 and/or Cx43 or their genetic variations in hypertension is unknown as human models have failed to show similar data.

Epigenetics

Genetic expression involves two main elements: the integrity of the DNA sequence (i.e., mutations), and the accessibility of the DNA to transcriptional enzymes (epigenetics). Mutations are heritable and involve intrinsic changes in the DNA sequence that alters the gene product, changing or obliterating the functionality of the gene product. In contrast, epigenetics is the study of alterations of gene expression, due to chemical modification of DNA base pairs that reduce their transcription by blocking or impairing the binding of polymerases. These changes account for tissue-specific gene expression, and thus, there are epigenetic differences between different tissues within the same individual. Furthermore, epigenetic modifications can change over time as individuals age or in response to environmental cues. Epigenetic modifications reduce the production of proteins and can persist over several cell divisions or throughout the life of the organism in somatic cells. While these changes are viewed as temporal, with an expectation of erasure during gametogenesis, there are clear examples of epigenetic changes that are passed along to offspring. There is increasing interest in exploring the role that epigenetics may play in the development and/or maintenance of hypertension. As we improve our understanding of the various site mutations in specific genes, the possibility exists that epigenetics plays an equally important role or even a dominant role in the development of hypertension. Both the applications and the molecular mechanisms of epigenetic modifications are the subject of considerable active research, and some excellent reviews are available [34–38].

In addition to mutations and variants in the nucleotide sequence of DNA that alter the functionality of the gene products, there are other elements that influence chromatin structure, such as methylation, phosphorylation, and acetylation of histone proteins that can alter transcription rates of genes that regulate blood pressure. Chromatin structure influences the accessibility of DNA to polymerases, and the extent to which DNA may enter a single-stranded conformation required for polymerase binding and thus gene expression. In addition, methylation of the nucleotides themselves can influence polymerase binding that initiates gene expression. These variations provide variations in gene expression and activity.

Epigenetic alterations in DNA methylation and histone modification have been associated with hypertension. For instance, while genetic mutations are correlated with hypertension, DNA methylation of the α-adducin (ADD1) promoter has been negatively correlated with essential hypertension. Patients with diminished methylation of the ADD1 promoter were found to have an increased chance of developing hypertension [39]. One explanation for this observation is that lower DNA methylation is associated with higher expression of α-adducin, resulting in increased activity and expression of the Na/K pump, which increases renal sodium reabsorption [39]. Furthermore, placentas from women with preeclampsia have been found to exhibit global alterations in DNA methylation.

Exercise has also been shown to alter methylation rates which are also accompanied by histone modification [40]. These epigenetic changes may explain why there is individual variation in exercise-induced blood pressure reduction, and they could prove useful to clinicians in the future to predict which patients may have a more favorable response to an exercise program. It has been suspected that traditional hypertension risk factors such as obesity, alcohol consumption, and smoking can also be accompanied by alterations in DNA methylation, which could be involved in the development of hypertension in certain individuals. The increased understanding of the epigenetics of hypertension may assist clinicians in identifying different forms hypertension that respond selectively to specific drugs. This differentiation would be based on the identification of patient's epigenome, allowing for earlier recognition of the potential to develop hypertension and could also result in a more focused treatment regimen, including nonpharmacologic treatment and/or lifestyle modification.

Recently, the expression of NKCC1 has been found to be unregulated in rat models, when exposed to elevated levels of angiotensin II. Measurements of NKCC1 messenger RNA (mRNA), as well as acetylated histone H3 (H3Ac), an activating histone code, and trimethylated histone H3 at lysine 27 (H3K27me3), a repressive histone code, revealed a positive correlation of NKCC1 mRNA and H3Ac with blood pressure. Given these data, it was suggested that NKCC1 was dysregulated via changes in histone modification [41]. However, it remains unclear whether these changes cause hypertension or are the result of the development of hypertension. While phosphorylation is a known element of histone modification, there is little evidence implicating this process in the genetics of hypertension. This lack of evidence does not imply a lack of role, but rather highlights a genetic area for future research.

While not part of the exome, and thus not part of the translational DNA, microRNAs (miRNAs) have been implicated in blood pressure control. These small single-stranded segments of noncoding RNA are found in plants and animals and function by binding to mRNAs in the cytoplasm by way of complementary base-pairing to form double-stranded RNA complexes that are degraded rather than translated into proteins. It is theorized that up to one third of the human genome is under miRNA control. It has been reported that two miRNAs, miR181a and miR663, regulate renin gene expression [42]. Furthermore, intrarenal expression of miR200a, 200b, 141, 429, 205, and 192 has also been associated with the development of hypertensive nephrosclerosis and their expression correlates with disease severity. Given that the vast majority of research has been focused on coding variations of the exons of candidate genes until very recently, more work is needed to investigate the role of epigenetics including

MiRNAs in hypertension and the target organ damage associated with hypertension.

Future Areas Involving the Genetics of Hypertension

Big Data

As the field of genetics has developed, results from multiple individual studies involving differing patient groups have increased our understanding of the human genome in relation to disease, including hypertension. These studies have largely revolved around population studies and employed various genetic technology/methodology such as GWAS in specific patient populations. While they have yielded important data, many are statistically underpowered and/or have studied limited populations, which can raise questions as to the hypertension phenotype being studied. Furthermore, as DNA sequencing technology becomes increasingly affordable and expedient, larger studies are being developed which address some of these limitations. Currently, investigators have two choices in designing genetic-based experiments. They can either investigate a limited number of patients deeply or screen a large number of patients for a limited number of genetic markers. Further work would be best suited if data could be merged from multiple studies already completed and/or those ongoing or proposed, such as the NCBI projects and international genomic databases. These efforts would require significant collaboration among investigators and public and private agencies, greater attention to the hypertension phenotype, and new methods of data analysis. Given the polygenetic nature of hypertension coupled with the interaction with environmental factors, it seems that efforts to collect and analyze "big genetic data" would be worth the effort. There could be a significant increase in the yield of future studies if the study population size were increased from 50,000 patients to 50 million patients, for instance. The recent announcement that the World Health Organization and Centers for Disease Control have identified hypertension as the first noncommunicable disease to address on a global basis, as has been done with communicable diseases such as tuberculosis, presents a rich opportunity to pursue "big data." This initiative aims to standardize the global treatment of hypertension with the goal of increasing the global control rate of hypertension and presents a tremendous opportunity to include a global genetic data component. Such a genetic initiative would help tailor future specific studies to understand to a greater extent the ethnic and racial variation, as well as, the phenotypic variation of hypertension.

Gene Cluster-Pathway Analysis

As previously mentioned, most studies to date have been designed to investigate specific candidate genes or genetic modifications, as well as the underlying mechanisms surrounding the development of monogenetic hypertension and hypotension. However, as the field has rapidly progressed, such studies have only incrementally increased our understanding of hypertension. Future studies would do well to evaluate gene clusters such as gene clusters involved with known hypertensive systems such as the sympathetic nervous system, the RAAS, or sodium retention systems, as well as cellular and signal transduction pathways involved in oxidative stress and inflammation.

Personalized Medicine

Much has been written about the use of genetic studies to predict individual drug responses with much greater specificity than has been previously possible. This takes two approaches, one involving pharmacodynamics and one involving pharmacokinetics.

In the pharmacodynamic approach, the genetic variation under study relates to the biomolecules that represent the drug target. The practical significance of genetic heterogeneity in the etiology of hypertension is that different patients will have different underlying defects. Once these underlying defects are understood, different pharmacologic agents can be designed to interact with these different drug targets. As an example of a successful pharmacodynamic approach to personalized medicine in hypertension, consider Liddle syndrome. In these patients, the disrupted gene is ENaC. Virtually all Liddle syndrome patients respond to well potassium sparing diuretics like amiloride.

In contrast, in the pharmacokinetic approach, the genetic variation under study is the patient's individualized ability to metabolize and excrete specific drugs. This approach enables the physician to adjust the dose in a patient-precise manner to ensure that the blood concentration of the drug stays within the therapeutic range. The body of knowledge around patient differences in capacity for drug metabolism and excretion, including drugs used in the treatment of hypertension, is already quite extensive [43].

A more complete knowledge of pharmacogenetics would aid the clinician in determining whether a patient who has traditionally been considered at intermediate risk is actually at low risk or high risk for developing hypertension and cardiovascular disease, what drugs are likely to be effective in treatment, and what dose will be required to maintain the patient's drug levels within the therapeutic range of the drug.

While GWAS have been useful, it is interesting to speculate that in the future these SNPs could be used to identify a patient's particular allele risk pattern and, when coupled with

BMI, age, and other traditional risk factors, give a more accurate assessment of their risk of developing hypertension and target organ damage. This would aid the clinician in determining whether a patient who was traditionally considered at intermediate risk is at low risk or high risk for developing hypertension and cardiovascular disease and assist in early detection and intervention.

Under current treatment methods, outpatient physicians select the appropriate antihypertensive medications after considering patient demographics, comorbidities, drug interactions, as well as ease of use. Despite being considered personalized medicine, there still remains a significant element of trial and error required in order to achieve adequate blood pressure control. The addition of genetic information during the synthesis of a treatment plan would further delineate underlying risk factors and could aid clinicians in appropriate antihypertensive drug selection and better tailor their therapeutic regimen to reflect the patient's genetic makeup.

Studies have already demonstrated the potential utility of this approach. It has been found that in individuals with the salt-sensitive allele, ADD1, diuretic therapy reduced the risk of myocardial infarct and stroke then when compared with alternative antihypertensives [22]. Additionally, certain β-adrenoreceptor polymorphisms are associated with an increased blood pressure reduction response to beta blockade and sodium sensitivity [17, 18, 28]. Additionally, it was recently demonstrated that variations within PRKCA, which encodes a serene-threonine protein kinase controlling a variety of cellular signaling pathways, influence interindividual variation in the blood pressure response to the thiazide diuretic, hydrochlorothiazide. Patients who carry the M235T polymorphism in the AGT gene exhibit a greater blood pressure lowering response to RAAS inhibition [16]. Furthermore, it may soon be possible for a clinician to prescribe exercise programs for individuals that are more likely to experience a significant blood pressure reduction [40].

Conclusion

The pathogenesis of hypertension is largely unknown and likely involves the complex interplay between genetic and environmental factors and interindividual heterogeneity. Clues from autosomal dominant genes associated with syndromic hypertension implicate biomolecules that modulate vessel constriction and dilation, salt/water homeostasis, the renin-angiotensin-aldosterone components, and G-protein signaling. Environmental agents both directly (e.g., sodium, stress, drugs, etc.) and indirectly via epigenetic mechanisms contribute to the phenotypic expression of hypertension. Several new genes identified through genome-wide association studies (e.g., HYT gene class) have been identified but not yet characterized with respect to their actions. While the study of the genetics of hypertension has made strides in recent years, the clinical application of genetics to the majority of individuals with essential hypertension has not met expectations. This disappointment may reflect the complexity of hypertension and the physiological elements that are disrupted in hypertension, the genetic heterogeneity of patients with respect to underlying causes, and the interplay of genetic, epigenetic, and environmental influences on phenotype. Further investigation of potential genetic targets, some of which were described in this review, is very likely to yield clues to advance our understanding of the development, detection, and treatment of hypertension.

Acknowledgments Donald J. DiPette, MD, was supported in part by the Health Sciences Distinguished Professorship, University of South Carolina, Columbia, SC, USA.

Compliance with Ethics Guidelines

Conflict of Interest Tariq Horani, Elizabeth Edwards, Donald DiPette, and Robert Best have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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