

Genomics and Pharmacogenomics of Salt-sensitive Hypertension

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Abstract: Salt sensitivity is estimated to be present in 51% of the hypertensive and 26% of the normotensive populations. The individual blood pressure response to salt is heterogeneous and possibly related to inherited susceptibility. Although the mechanisms underlying salt sensitivity are complex and not well understood, genetics can help to determine the blood response to salt intake. So far only a few genes have been found to be associated with salt-sensitive hypertension using candidate gene association studies. The kidney is critical to overall fluid and electrolyte balance and long-term regulation of blood pressure. Thus, the pathogenesis of salt sensitivity must involve a derangement in renal NaCl handling: an inability to decrease renal sodium transport and increase sodium excretion in the face of an increase in NaCl load that could be caused by aberrant counter-regulatory natriuretic/antinatriuretic pathways. We review here the literature regarding the gene variants associated with salt-sensitive hypertension and how the presence of these gene variants influences the response to antihypertensive therapy.

Keywords: Hypertension, kidney, pharmacogenomics, salt sensitivity.

INTRODUCTION

The prevalence of hypertension in the adult population worldwide is more than 26% and is estimated to increase to 30% by 2025, constituting an important public health challenge in industrialized and developing countries [1]. The prevalence of hypertension varies with age, sex, and ethnicity and is also affected by behavior such as the intake of dietary sodium and potassium. Excess dietary salt intake is a predominant cause of hypertension. The increase in blood pressure with an increase in sodium intake occurs in both normotensive and hypertensive subjects and is predictive of increased cardiovascular events and mortality irrespective of basal blood pressure levels [2, 3]. Salt sensitivity is estimated to be present in 51% of the hypertensive and 26% of the normotensive populations [4].

The individual blood pressure response to salt is heterogeneous and possibly related to inherited susceptibility. Although the mechanisms underlying salt sensitivity are complex and not well understood, genetics can determine the blood response to salt intake [5, 6]. Research in the field has concentrated on the identification of common allelic variants of candidate genes for hypertension in relation to the salt-sensitive phenotype and the pathogenic role of gene-gene interaction with the aim to distinguish salt-sensitive from salt-resistant subjects. So far, however, genome-wide association studies have identified genes that influence only 2% of blood pressure variability and have not identified

genes that influence the salt sensitivity of blood pressure. Only a few genes have been found to be associated with salt-sensitive hypertension using candidate gene association studies.

The kidney is critical to overall fluid and electrolyte balance and long-term regulation of blood pressure [7]. The identification of rare monogenic forms of hypertension associated with abnormalities of renal tubular sodium handling [8] highlighted the important role of renal alterations in salt-sensitive hypertension but cannot explain the high incidence of salt sensitivity, especially in normotensive humans. These observations however indicate that the pathogenesis of salt sensitivity must involve a derangement in renal NaCl handling: an inability to decrease sodium transport and increase sodium excretion in the face of an increase in NaCl load that could be caused by aberrant counter-regulatory natriuretic/antinatriuretic pathways [9]. The sympathetic nervous system and the renin-angiotensin system (RAS) [10-12] are examples of antinatriuretic pathways. An important counter-regulatory natriuretic pathway is afforded by the renal autocrine/paracrine dopamine system, aberrations of which are involved in the pathogenesis of hypertension [13-15].

GENETIC VARIANTS ASSOCIATED WITH SALT SENSITIVITY OF BLOOD PRESSURE

This review updates the comprehensive reviews of the genetics of salt sensitivity by Strazzullo and Galletti in 2007 [8] and Sanada *et al.* 2011 [5].

Table 1 lists the genetic variants reported to be associated with salt sensitivity, by themselves or in association with others, in studies replicated in one or more cohorts or

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Table 1. Genes associated with salt-sensitive essential hypertension.

Candidate Gene	Associated Variant	References
Genes associated with increased renal sodium transport or vascular reactivity		
Angiotensinogen (<i>AGT</i>)	rs5051 (G6A) M235T (rs699)	[8, 29, 54]
Angiotensin-converting enzyme (<i>ACE</i>)	Indel polymorphism	[8, 29]
Angiotensin II type 1 receptor (<i>AGTR1</i>)	rs4524238	[55]
Aldosterone synthase (<i>CYP11B2</i>)	rs1799998 (T-344C)	[56, 57]
11 β -Hydroxysteroid dehydrogenase type 2 (<i>HSD11B2</i> , <i>11βHSD2</i>)	(rs45598932 (G-209A))	[58]
Lysine-specific demethylase 1 (<i>LSD-1</i>)	rs671357 rs587168	[17]
Striatin (<i>STRN</i>)	rs2540923	[18]
β_2 adrenergic receptor (<i>ADRB2</i>)	rs1042714 (C79G) rs1042713 (A46G)	[59]
Chloride channel, Kidney A (<i>CLCNKA</i>)	rs1010069 rs1805152 rs848307 rs1739843	[60]
Epithelial sodium channel gamma subunit1 (ENaC gamma subunit1) (<i>SCNN1G</i>)	rs5718 (G-173A) rs4073930 rs7404408 rs4299163 s4073291 rs5735 rs4499238	[34]
Neural precursor cell expressed developmentally down-regulated 4-like (<i>NEDD4L</i>)	rs2288774 rs4149601	[45, 61]
Protein kinase, lysine-deficient 1 (<i>WNK1</i>)	rs880054	[45]
Serum- & Glucocorticoid-Regulated Kinase (<i>SGK1</i>)	rs2758151 rs9402751	[62, 63]
Ste20-related proline-alanine-rich kinase (<i>STK39</i>)	rs6749447 rs3754777 rs1937506 rs35929607	[64-67]
Sodium bicarbonate exchanger (<i>SLC4A5</i>)	rs7571842 rs10177833	[19]
Uromodulin (<i>UMOD</i>)	rs13333226 rs4293393	[20, 21]
ATPase, Ca ⁺⁺ transporting (<i>ATP2B1</i>)	rs2681472	[67]
Cytochrome P450 3A5 (<i>CYP3A5</i>)	rs776746 (A6986G)	[68]
Guanine nucleotide binding protein, subunit 3 (<i>GNB3</i>)	rs1129649 (C825T)	[69]
Potassium dependent Na ⁺ /K ⁺ /Ca ²⁺ exchanger type 3 NCKX3 (<i>SLC24A3</i>)	rs3790261	[70]
Sodium Calcium exchanger 1 NCX1 (<i>SLC8A1</i>).	rs434082	[70]
Endothelin converting enzyme 1 gene (<i>ECE1</i>)	rs213014	[71]
NAD(P)H oxidase p22 ^{phox} (<i>CYBA</i>)	rs4673 (C242T)	[72, 73]
Fibroblast growth factor 5 (<i>FGF5</i>)	rs16998073	[67]
Branched chain aminotransferase 1 (<i>BCAT1</i>)	rs7961152	[67]
α -adducin (<i>ADD1</i>)	rs4961 (G460T) rs17833172	[42, 74]

Table 1. contd....

Candidate Gene	Associated Variant	References
Genes associated with decreased renal sodium transport or vascular reactivity		
Endothelin receptor type B (<i>EDNRB</i> , <i>ETB</i>)	rs5351 (G1065A)	[8, 29]
Nitric oxide synthase 3 (<i>NOS3</i>)	rs2070744 (T-786C)	[75, 76]
Dimethylarginine dimethylaminohydrolase 1 (<i>DDA1</i>)	rs11161637	[17, 75]
cGMP-dependent protein kinase 1 (<i>PRKG1</i>)	rs7897633	[70]
Bradykinin receptor B2 (<i>BDKRB2</i>)	rs11847625	[71]
von Willebrand factor (<i>VWF</i>)	rs2239153	[77]
20-HETE synthase (<i>CYP4A11</i>)	T8590C	[78]
G protein-coupled receptor kinase 4 (<i>GRK4</i>)	R65L (rs296036) A142V (rs1024323) A486V (rs1801058)	[5, 19, 22, 24, 47]

controlled studies involving large number of subjects (GenSalt, HyperPATH, HapMap).

Genes Related to Increased Renal Sodium Transport or Vascular Reactivity

Renin-angiotensin Aldosterone System (RAAS)

The RAAS is the most important regulator of renal sodium transport and the major system involved in the increase in renal sodium transport, especially under conditions of sodium deficit [10, 16]. Only two polymorphisms of *AGT*, one in *ACE*, one in *AGTR1*, one in *CYP11B2*, and one in *11βHSD2*, the enzyme that inactivates 11-hydroxysteroid in the kidney protecting the mineralocorticoid receptor from occupation by glucocorticoids, have been reported to be associated with salt-sensitive hypertension. Polymorphisms in the lysine-specific demethylase 1 gene, an epigenetic regulator of aldosterone production, were also found associated to salt sensitivity [17].

Striatin is a protein that regulates the nongenomic actions of the estrogen receptor- α and mineralocorticoid receptor. *STRN* rs2540923 has been reported to be associated with salt sensitivity in humans [18].

Sympathetic Nervous System

Increased sympathetic activity has been demonstrated in salt-sensitive hypertension. Although several polymorphisms in the enzymes involved in the synthesis of catecholamines and their receptors have been described to be associated with essential hypertension, only a haplotype of the *ADRB2* has been associated with salt sensitivity.

Renal Ion Transport

Renal ion channels and transporters are common final pathways in the regulation of the transport of sodium and other ions. Common variants of the amiloride sensitive epithelial sodium channel gamma subunit1 (*ENaCγ*), and several in genes encoding *ENaC* regulators such as *NEDD4L*, *WNK1*, and *SGK1*, as well as the renal chloride

channel *CLCNA*, are associated with hypertension and salt sensitivity. Polymorphisms in the *STK39* gene that encodes a serine/threonine kinase that interacts with *WNK* kinases and cation-chloride cotransporters have also been identified to be associated with salt sensitivity of blood pressure. Similarly, variants in the *SLC4A5* gene that codes for NBCe2, an electrogenic Na^+ -bicarbonate co-transporter that helps maintain the homeostasis of intracellular pH by co-transporting three bicarbonate anions for each Na^+ cation are also associated with salt sensitivity [19]. Uromodulin, also known as Tamm-Horsfall protein, is expressed in the thick ascending limb of Henle and has been linked to water/electrolyte balance. A polymorphism in the uromodulin gene (rs13333226) is associated with hypertension and lower fractional excretion of sodium [20]. Another polymorphism rs4293393 is associated with increased diastolic blood pressure and salt sensitivity [21].

Genes that Regulate Vascular Smooth Muscle Tone

Polymorphisms of genes that influence the vascular tone through an increase in the concentration of cytoplasmic calcium (Ca^{++}), such as *SLC24A3* and *SLC8A1* or endothelial function such as *ECE1* are associated with salt-sensitive hypertension.

Reactive Oxygen Species (ROS)

In non-phagocytic cells, ROS regulate vascular tone, cell growth, and inflammation and may be important mechanisms that contribute to the maintenance of high blood pressure initiated by other primary processes. Some polymorphisms in genes regulating the production of ROS and inflammation such as NAD(P)H oxidase p22^{phox} (*CIBA*), *FGF5*, and *BCAT1*, a marker of oxidative stress, are also associated with salt-sensitive hypertension.

Adducins are cytoskeletal proteins that regulate the membrane organization of spectrin-actin which is involved in the internalization and recycling of Na^+/K^+ -ATPase. Although wild-type *ADD1* has only a minimal effect on Na^+/K^+ -ATPase, some of its variants increase Na^+/K^+ -ATPase

activity and therefore increase renal sodium transport, are associated with salt-sensitive hypertension.

Genes Related to Decreased Renal Sodium Transport or Vascular Reactivity

Vasoactive Peptides/Substances

Endothelin mediates vasoconstriction but can cause also vasodilation by increasing NO production from endothelial cells and decrease sodium transport. *ETBR* in vascular smooth muscle cells mediate vasoconstriction, while *ETBR* in endothelial cells mediate vasodilatation.

Polymorphisms in two genes related to NO synthesis, *NOS3* and *DDAH1*, and in one involved in NO signaling, *PRKG1*, are associated with salt sensitivity. Bradykinin causes vasodilation through the *BDKRB2*. 20-HETE increases blood pressure by vasoconstriction but can also decrease blood pressure by decreasing renal sodium transport, especially at the proximal tubule and thick ascending limb of Loop of Henle. The loss-of-function in 20-HETE synthase (*CYP4A11*) 8590C allele is associated with salt sensitivity.

Dopaminergic System

Dopamine produced in the kidney (mainly by proximal tubules) acts in an autocrine/paracrine manner to regulate renal ion transport. The inhibition of renal transport of sodium and other ions occurs in multiple segments of the nephron, including the proximal and distal convoluted tubule, thick ascending limb of Loop of Henle, and collecting ducts.

The inhibitory effect of dopamine and D1-like receptor agonists on sodium transport is impaired in hypertension and the decreased function of DIR in hypertension may be related to a state of constitutive desensitization due to the presence of activating variants of GRK4, including GRK4 R65L, A142V and A486V. Several studies in different ethnic groups have shown that *GRK4* gene variants are associated with human essential hypertension and salt sensitivity [22-25]. Salt-sensitive hypertensive Japanese subjects carrying at least three *GRK4* gene variants have an impaired natriuretic response to a dopaminergic drug and salt-sensitive hypertension can be correctly predicted in 94% of the cases. Sodium excretion is inversely related to the number of *GRK4* variants in hypertensive subjects, and the natriuretic response to dopaminergic stimulation is impaired in normotensive individuals having *GRK4* gene variants [24]. The presence of the different *GRK4* variants depends on ethnicity. GRK4 486V is more frequent in Asians (47%) than in Caucasians (40%), Hispanics (28%), or African Americans (19%). By contrast, GRK4 65L and GRK4 142V are more frequent in African Americans (47% and 45%, respectively) than in the other ethnic groups: Caucasians (35% and 40%), Hispanics (25% and 29%), and Asians (7% and 20%) [26]. In Korean children, the best combination to predict obesity as sodium intake increased, was *SLC12 A3*, *ACE* and *GRK4 A486V* in boys, and *CYP11 β -2* and *GRK4 A486V* in girls [27].

A particular phenotype is caused not only by one particular gene but by gene-gene interactions which may affect the same or different physiological pathways. Thus, the susceptibility to salt-sensitive hypertension may be

Table 2. Gene-gene interactions in salt-sensitive hypertension.

Gene Variant	Interacting with	References
Angiotensin-converting enzyme (<i>ACE</i>) In/del	<i>EDNRB</i> 1065GG <i>HSD11B2</i> G534A	[8, 29, 79, 80]
β_2 adrenergic receptor <i>ADRB2</i> C79G <i>ADRB2</i> Q27E	<i>ADRB2</i> A46G <i>TH</i> rs2070762	[25, 59]
Neural precursor cell expressed developmentally down-regulated 4-like (<i>NEDD4L</i>) rs2288774	<i>NEDD4L</i> rs4149601	[61]
Potassium dependent Na ⁺ /K ⁺ /Ca ⁺⁺ exchanger type 3 (<i>NCKX3</i>) <i>SLC24A3</i> rs3790261	Sodium Calcium exchanger 1 <i>NCX1</i> <i>SLC8A1</i> rs434082	[70]
Chloride channel, Kidney A <i>CLCNKA</i> rs1010069	<i>CLCNKA</i> rs12126269	[60]
Cytochrome P450 3A5 <i>CYP3A5</i> rs776746 (A6986G)	<i>ABCB1</i>	[68]
α -Adducin <i>ADD1</i> rs4961 (G460T)	<i>WNK1</i> rs1159744 and <i>NEDD4L</i> rs4149601 <i>ACE DD</i> and <i>CYP11B2</i> rs1799998 (-344C)	[25, 80]
G protein-dependent receptor kinase 4 (<i>GRK4</i>) GRK4 486V GRK4 486V GRK4 486V GRK4 486V GRK4 486V GRK4 65L	GRK4 142V, GRK4 65L predict salt-sensitive hypertension (94%) <i>TH</i> 2070762 and <i>ADRB2</i> Q27E <i>GNB3 A-350G</i> <i>CYP11B2*1C</i> <i>GKR4 142V</i> , <i>GNB3</i> and <i>PAI-1</i> <i>ACE VD</i>	[19, 24, 25, 27, 82]

determined not only by specific gene variants but also by combinations of multiple gene variants. Table 2 lists reported gene-gene interactions in salt-sensitive hypertension.

PHARMACOGENOMICS OF SALT-SENSITIVE HYPERTENSION

The inter-individual variability and abnormal response to antihypertensive drugs may be partially accounted for by genetic polymorphisms. Common gene variants may influence the response to diuretics, β -adrenergic blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Pharmacogenomics studies the genetic basis for variation in drug response [28] with the aim of predicting whether a patient will have a good response to a drug, an adverse response to a drug, or no response at all, and designing therapeutic strategies on the bases of matching the pathophysiology of the increase in blood pressure to the pharmacological action of the drug prescribed. However, the literature in the field is limited, in particular regarding salt-sensitive hypertension.

Genes Related to Increased Renal Sodium Transport or Vascular Reactivity

The *AGT* M235T polymorphism was associated with a decrease in blood pressure after a decrease in sodium intake. Carriers of TT or MT genotype had lower blood pressure after sodium restriction compared with carriers of the MM genotype [29, 30]. The *ACE* indel (I/D) polymorphism, DD in men and II and ID in women [31], was associated with the systolic blood pressure response to hydrochlorothiazide in a Han Chinese population of mild/moderate with essential hypertension. In the same population, CYP11B2 -344T/C was not found to be associated with the response to the diuretic [32]. Interestingly, neither *AGT* M235T nor *ACE* I/D was associated with antihypertensive effects of RAS blockade [33].

Each of the ENaC γ gene variants, *SCNN1G* rs4073930, rs4073291, rs404408, rs5735, rs4299163, and rs4499238, had a 1.09 to 1.33 mm Hg decrease in systolic blood pressure in response to low sodium diet for 7 days [34].

NEDD4L negatively regulates NCC and the renal epithelial sodium channel (ENaC). *NEDD4L* rs4149601 has been associated with a 6.1 mm Hg reduction of systolic blood pressure in response to hydrochlorothiazide [35]. *NEDD4L* rs4149601 was also associated with a 4.5 mm Hg reduction in systolic blood pressure with β -adrenergic blockade or diuretic monotherapy in another study; there was no influence on the response to the calcium channel blocker, diltiazem [36]. A greater blood pressure response to hydrochlorothiazide was observed with increasing copies of the G-C haplotype of *NEDD4L* (for the SNPs rs4149601 and rs292449, respectively) [37].

In Finnish males, *STK39* rs6749447 was associated with a lower systolic and diastolic blood pressure response to losartan than bisoprolol, hydrochlorothiazide, or amlodipine [38]. In another study, *STK39* rs6749447, rs3754777, and rs35929607 were not associated with a blood pressure response to thiazides [39]. Why *STK39* rs6749447 is associated with a better blood pressure lowering effect to an

AT1R blocker but not to a diuretic [38, 39] cannot be explained at this time. However, angiotensin II signaling related to NCC is dependent on WNK4-SPAK (encoded by *STK39*) signaling [40]. *GNB3* C825T, alone or in combination with two other polymorphisms A3882C and G5249A, was associated with a blood pressure response to atenolol in women but not in men [41]. *ADD1* rs4961 has been reported to be associated with hypertension in several but not all ethnic groups [42]. *ADD1* rs4961 predicted a 14 mm Hg decrease in blood pressure in response to a ouabain antagonist in some studies [43, 44] and a 4 mm Hg greater decrease in blood pressure (variant vs. wild-type) in response to one month of diuretic treatment [45]. The latter response was observed in the presence of two other variants that are also associated with salt sensitivity, i.e., *WNK1* rs880054, *NEDD4L* rs4149601 [45].

Genes Related to Decreased Renal Sodium Transport or Vascular Reactivity

GPR83 rs3768785 was associated with a good response to the AT1R blocker, candesartan, but not to hydrochlorothiazide in whites but good response to both drugs in blacks [46].

Constitutively active variants of *GRK4* (rs296036, rs1024323, rs1801058) are associated with hypertension with or without salt sensitivity [19, 47, 48]. *GRK4* rs2960306 and *GRK4* rs1024323 haplotype were predictive of a failure to decrease mean arterial pressure to ≤ 107 mm Hg in response to β -adrenergic blockade in African-American men with early hypertensive nephrosclerosis. *GRK4* rs1024323 by itself was associated with a response to β -adrenergic blockade mean arterial pressure < 107 mm Hg, albeit a slow one [49]. In two cohorts of American population with essential hypertension without renal disease, as the number of individual *GRK4* SNPs 296036 (R>L) and 1024323(A>V) increased, the blood pressure response to β -adrenergic blockade in a mixed population of black and white individuals decreased, while the opposite was observed with the wild-type carriers [50]. Whether or not the different results between these two studies are related to ethnicity or the presence or absence of renal disease remains to be determined. In South African blacks, *GRK4* R65 or *GRK4* A142 predicted a good blood pressure response to a decrease in salt intake for 8 weeks, while *GRK4* 65L or *GRK4* 142V predicted a limited response to reduced salt intake [51]. The presence of at least three *GRK4* allele variants (65L, 142V, and 486V), relative to those with fewer than three, was associated with a better response to diuretic therapy [52]. Hypertensive Japanese showed an allelic and genotypic association of *GRK4* 142V with enhanced response of blood pressure to AT1 receptor blockers. Although individuals with one or two copies of *GRK4* 142V did not show a difference in the achievement of blood pressure goal compared to those with no *GRK4* variants, they had a significantly greater decrease in systolic blood pressure in response to AT1 receptor blockers than non-carriers [53].

The slow progress in the knowledge on the genetics of salt-sensitive hypertension and the pharmacogenetics of abnormal response to antihypertensive drugs is related to the complexity of the genome regulation and the heterogeneity of hypertension. The identification of genetic variants related

to blood pressure regulation may reveal new therapeutic drug targets.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was funded by grants from the US National Institutes of Health, R01DK090918, P01HL074940, P01HL068686, R01HL092196, R37HL023081 and R01DK039308.

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