Sodium Sensitivity of Blood Pressure in Chinese Populations

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Abstract

Hypertension is an enormous public-health challenge in the world due to its high prevalence and consequent increased cardiovascular disease morbidity and mortality. Observational epidemiologic studies and clinical trials have demonstrated a causal relationship between sodium intake and elevated blood pressure (BP). However, BP changes in response to sodium intervention vary among individuals — a trait called sodium sensitivity. This paper aims to review the recent advances in sodium-sensitivity research in Chinese and other populations. Older age, female gender, and black race are associated with high sodium sensitivity. Both genetic and environmental factors influence BP sodium sensitivity. Physical activity and dietary potassium intake are associated with reduced sodium sensitivity while obesity, metabolic syndrome and elevated BP are associated with increased sodium sensitivity. Familial studies have documented a moderate heritability of sodium sensitivity. Candidate gene association studies, genome-wide association studies, whole-exome, and whole-genome sequencing studies have been conducted to elucidate the genomic mechanisms of sodium sensitivity. The Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study, the largest family-based feeding study to date, was conducted among 1906 Han Chinese in rural northern China. This study showed that approximately 32.4% of Chinese adults were sodium sensitive. Additionally, several genetic variants were found to be associated with sodium sensitivity. Findings from the GenSalt Study and others indicate that sodium sensitivity is a reproducible trait and both lifestyle factors and genetic variants play a role in this complex trait. Discovering biomarkers and underlying mechanisms for sodium sensitivity will help to develop individualized intervention strategies for hypertension.

Introduction

Hypertension is an enormous public health challenge due to its high prevalence and consequent increased cardiovascular disease and related premature death and disability worldwide.^{1–3} Globally, the prevalence and absolute burden of hypertension increased from 25.9% and 921 million in 2000 to 31.1% and 1.39 billion in 2010.¹ A large number of

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observational epidemiological studies have documented a positive and significant association between dietary sodium intake and high blood pressure (BP).^{4,5} Randomized controlled clinical trials have provided unbiased evidence for a causal relationship between reduced dietary sodium intake and BP reduction.^{6,7}

Kawasaki et al.⁸ and later on Weinberger et al.⁹ were among the first to recognize the heterogeneity of BP in response to sodium intake and develop the concept of sodium sensitivity in humans. Renal sodium handling and vascular endothelium have been proposed as important mechanisms regulating sodium sensitivity of BP in humans.¹⁰ Sodium sensitivity of BP is not only associated with hypertension but also independently associated with cardiovascular disease and mortality.^{11,12} A prospective cohort study conducted by Weinberger and colleagues used rapid sodium loading and depletion methods to identify sodium sensitivity and found that sodium sensitivity of BP is associated with mortality in both normotensive and hypertensive subjects.¹¹ Morimoto and colleagues carried out a retrospective study of cardiovascular events in patients with essential hypertension who had a measured sodium sensitivity by dietary sodium intake in clinic.¹² They observed that cardiovascular events occurred more frequently in patients with documented sodium sensitivity of BP.

Examining the genetic and environmental determinants of sodium sensitivity of BP has important public health and clinical implications. Establishing a relationship between genetic variants and sodium sensitivity will help identify individuals at high risk for developing hypertension whom could also benefit from a low sodium dietary intervention and/or pharmaceutical treatment with novel genotype-based drugs. In addition, identifying genes that specifically interact with dietary sodium intake on the regulation of BP will contribute significantly to our knowledge about physiological pathways underlying hypertension. Identifying genetic variants associated with sodium sensitive hypertension will also aid in the development of new antihypertensive medications that target biological pathways related to sodium metabolism. From a public health standpoint, individuals with a modifiable genetic risk of hypertension could be identified prior to disease development, and effective and appropriate lifestyle modifications or novel pharmaceutical therapies could be implemented for primary prevention. Advances in this area of medicine could significantly enhance the clinical effectiveness of patient care and population based prevention of hypertension.

In this review paper, we aim to examine the current knowledge of sodium sensitivity in Chinese and other populations, including testing methods and reproducibility of sodium sensitivity, proportion of sodium sensitivity in populations, and genetic and lifestyle determinants of sodium sensitivity.

Definition and Testing of Sodium Sensitivity

The definition of sodium sensitivity varied between studies. It is most often defined as a proportional change (i.e., 3% to 10%) or an absolute change (i.e., 3 to 10 mm Hg) in mean arterial pressure during sodium intervention. Currently, two common methods have been used to assess sodium sensitivity of BP. The first is to measure the response of BP to low and high dietary sodium intake over one to two weeks. The Genetic Epidemiology

Network of Salt Sensitivity (GenSalt) study, which was a large family-based dietary feeding study, used this method to measure sodium sensitivity (Figure 1).¹³ Study participants received a low-sodium diet (3 grams of sodium chloride or 51.3 mmol of sodium per day) for 7 days, followed by a high-sodium diet (18 grams of sodium chloride or 307.8 mmol of sodium per day) for an additional 7 days. BP and urinary sodium excretion were measured on the last 3 days of each week. In general, the dietary approach is believed to be more clinically relevant and is considered the gold standard for the characterization of sodium sensitivity.

Another method is to assess BP response to rapid sodium loading and depletion. Weinberger and colleagues using a protocol that began with the intravenous administration of 2 L normal (0.9%) saline over 4 hours in the morning. BP was measured at the completion of the infusion at noon. On the following day, sodium and volume depletion were induced by a 10 mmol sodium diet and three doses of oral furosemide (40 mg every 8 hours). BP was measured again in the following morning. Sodium sensitivity of BP was defined as a decrease in mean arterial pressure ≥ 10 mm Hg, and salt resistance was defined as a decrease <6 mm Hg.¹¹

Reproducibility of Sodium Sensitivity

A few studies have tested the long-term reproducibility of sodium sensitivity of BP.^{14,15} Sharma et al used mean arterial pressure response after a reduced sodium intake (from 220 to 20 mmol/day) >3 mmHg to define sodium sensitivity. They reported the reliability of classification of sodium sensitivity by the κ statistic was 0.87, implying a strong agreement between the two responses to dietary sodium intake.¹⁴ In the GenSalt Study, the low and high dietary sodium interventions were repeated among 487 Chinese adults 4.5 years after the original test using the identical study protocol.¹⁵ BP responses to dietary intervention in the initial and later repeated studies were highly correlated. For example, the correlation coefficients for systolic BP levels were 0.77 at baseline, 0.79 during low-sodium, and 0.80 during high-sodium interventions (all $P < 0.0001$). The correlation coefficients for systolic BP changes were 0.37 from baseline to low sodium and 0.37 from low-sodium to high-sodium intervention (all $P < 0.0001$). These data suggest that BP responses to dietary sodium interventions have long-term reproducibility and stable characteristics in the general population.¹⁵

Proportion of Sodium Sensitivity in Chinese and Other Populations

BP response to dietary sodium intake in human subjects is a continuous and normally distributed trait. The distribution of BP responses to low and high dietary sodium interventions from the GenSalt Study are shown in Figure 2.¹³ These data show that BP responses to dietary sodium intake were normally distributed and no evidence for a bimodal distribution in this population was found. Both systolic BP and diastolic BP decreased during the low-sodium intervention and increased during the high-sodium intervention among majority of participants.¹³ Using a cut-off to categorize subjects as sodium sensitive or sodium resistant is arbitrary. If sodium sensitivity is defined as an absolute change of 5 mm Hg or more in mean arterial pressure, 33.9% of participants during the low-sodium intervention and 32.4% during the high-sodium intervention would have met the criteria. If a

proportional change of 5% or more in mean arterial pressure was as definition of sodium sensitivity, 38.7% of participants would have met the criteria during the low-salt intervention and 39.2% during the high-salt intervention.¹³

The proportion of sodium sensitivity of BP among various populations is shown in Table 1. Most of these studies were conducted in hypertensive patients with a small sample size.^{8,1,16,19} Different study protocols were employed, e.g., dietary sodium intake increased from 9 to 249 mmol per day in some studies^{8,16} and from 70 to 345 mmol per day in others.¹⁷ In addition, sodium sensitivity was defined as the difference in mean arterial pressure between low and high-sodium interventions 10% or 10 mm Hg in some studies^{8,16–19,21} or 3% or 3 mm Hg in others^{14,20}. Using a definition of mean arterial pressure 10% or 10 mm Hg, the proportions of sodium sensitivity varied from 32% to 64% among individuals with hypertension and 0% to 50% among individuals with normal BP.^{18,21}

Sodium Sensitivity by Age, Sex, and Race/Ethnicity

Much epidemiological evidence suggests that the age-related increases in BP may be related to sodium sensitivity due to age-related decrease in renal sodium handling.^{22,23} Miller and colleagues found that BP response to the manipulation of dietary sodium was correlated with age being higher among those >40 years old in normotensive adults.²⁴ Hurwitz and colleagues reported that every 10 years of age was associated with a 2.4 mm Hg increase in sodium sensitivity of systolic BP in hypertensive patients.²⁵ In the GenSalt Study, systolic BP increased 4.3, 5.7, and 7.4 mm Hg from low-sodium to high-sodium interventions among individuals aged <35, 35–44, and ≥45 years ($P<0.0001$ for trends).¹³

The GenSalt Study and others have shown that BP responses to dietary sodium intervention were more pronounced in women than in men.^{13,26,27} In the GenSalt Study, BP responses to high-sodium interventions were significantly greater in women than in men: 6.4 versus 5.2 mmHg for systolic and 3.1 versus 1.7 mmHg for diastolic (all $P<0.001$). Physiological studies have suggested that female hormones (estrogen and progesterone) might be associated with increased renal sodium reabsorption and water retention.^{28,29} In addition, the GenSalt Study suggests that genes encoding sex hormones could have important influences on the sodium sensitivity of BP.³⁰

Previous studies have documented that sodium sensitivity is more common among individuals of African-American descent.^{21,31} In the DASH-sodium trials, the decrease in BP associated with reduced sodium intake was more pronounced in normotensive African Americans.³¹ Wright et al. reported the prevalence of sodium sensitivity was similar in both black and white normotensives but increased in African Americans hypertensives.²¹ The reason for this difference in race may be because blacks have an intrinsic reduction in the ability to excrete sodium compared with whites³².

Determinations of Sodium Sensitivity

Usual blood pressure levels—Individuals with hypertension have a greater BP response to changes in sodium intake than individuals without hypertension.^{9,13,21} Weinberger and colleagues found that sodium sensitivity of BP was more common in

hypertensive than in normotensive subjects.⁹ In GenSalt Study, He and colleagues indicated that BP responses to dietary sodium intervention increased with age and higher baseline BP levels, especially for systolic BP.¹⁰ In the GenSalt Study, systolic BP increased 4.1, 5.5, and 7.7 mm Hg from low-sodium to high-sodium intervention among individuals with baseline BP <120/80, 120–139/80–89, and 140/90 mm Hg ($P < 0.0001$ for trends).¹³

Cold pressor test—The cold pressor test, which measures the response of BP to the stimulus of external cold, has been used as a standard measure for characterizing sympathetic nervous system activity in response to stress in normotensive and hypertensive subjects and has been suggested to predict the subsequent risk of hypertension in normotensives.^{33–35} Previous studies have also suggested that sympathetic nervous system activity might play a fundamental role in determining sodium sensitivity of BP.³⁶ In the GenSalt Study, a dose-response relationship between BP responses to cold pressor and dietary sodium interventions was identified.³⁷ Systolic BP responses by the quartiles of area-under-the-curve of response to cold pressor were –2.6, –4.6, –5.7, and –8.5 mm Hg during low-sodium intervention and 4.1, 4.4, 4.4, and 6.3 mm Hg during high-sodium intervention (all $p < 0.001$ for trends). These results indicated that BP response to cold pressor was associated with sodium-sensitivity. The GenSalt follow-up study indicated that BP response to the cold pressor is a reproducible measure of cardiovascular reactivity to stress.³⁹

Obesity—In addition to increasing the risk of hypertension, obesity has been linked to sodium sensitivity of BP.^{40–42} Rocchini and colleagues reported that obese adolescents had a significantly larger reduction in mean arterial pressure (–12 mm Hg) than non-obese adolescents (1 mm Hg) after successive two-week periods of a high-salt diet (>250 mmol of sodium per day) and a low-salt diet (<30 mmol per day).⁴⁰ Uzu and colleagues reported that central obesity was an independent risk factor for sodium-sensitive hypertension (odds ratio, 1.41; 95% confidence interval, 1.04–1.91).⁴¹ In GenSalt study, waist circumference was significantly associated with greater BP responses to dietary sodium intake.⁴² Abdominal obesity might be especially important in determining sodium sensitivity of BP primarily due to altered insulin resistance and renal tubular sodium handling.⁴³

Metabolic syndrome—Metabolic syndrome, a cluster of metabolic disorders including central obesity, insulin resistance, hyperglycemia, dyslipidemia, and elevated BP, is strongly associated with sodium sensitivity.^{41,42,44} Hoffmann and colleagues reported that reducing dietary salt from a usual intake of 8.2 g/day to 2.3 g/day lowered systolic BP by 8.7, 6.0, 3.4, 1.1, and 1.0 mm Hg, respectively, among individuals with 4–5, 3, 2, 1, and 0 components of the metabolic syndrome ($p < 0.0001$).⁴⁴ In the GenSalt Study, multivariable-adjusted mean changes (95% CIs) in BP were significantly greater (all $p < 0.0001$) among participants with metabolic syndrome compared to those without: 6.51 (5.76, 7.26) versus 4.55 (4.26, 4.84) for systolic BP and 3.25 (2.56, 3.94) versus 1.69 (1.42, 1.96) for diastolic BP during the high-sodium intervention.⁴² In addition, participants with 4 or 5 components of metabolic syndrome had a 3.13-fold increased odds (95% CI 1.80, 5.43) of sodium sensitivity during the high-sodium intervention. The underlying mechanism of increased sodium sensitivity in individuals with metabolic syndrome is not fully understood. Insulin resistance and

concomitant compensatory hyperinsulinemia might lead to sodium retention and extracellular fluid volume expansion, thereby increasing BP responses to sodium intake.^{45,46}

Physical activity—Prospective cohort studies reported that physical activity was significantly and inversely associated with the risk of hypertension⁴⁷ and randomized controlled trials documented that physical activity lowered BP in both normotensive and hypertensive individuals.⁴⁸ In the GenSalt Study, physical activity was significantly, independently, and inversely related to sodium sensitivity of BP, with a graded dose-response association between lower levels of physical activity and higher sodium sensitivity.⁴⁹ This protective effect might occur through several potential mechanisms, such as reduction of insulin resistance, improvement of endothelial function, and inhibition of sympathetic nervous system activity.⁴⁶

Potassium intake and diet—Randomized clinical trials documented that potassium intake lowers BP in both hypertensive and normotensive individuals.⁵⁰ In addition, dietary potassium intake modified BP responses to dietary sodium intake.^{51,52} Morris and colleagues tested the effects of potassium supplementation on sodium sensitivity in 38 healthy normotensive men who consumed a low sodium (15 mmol/day) and potassium (30 mmol/day) diet. Supplementing potassium up to 70 mmol/day attenuated BP response to sodium increase and abolished BP response at levels up to 120 mmol/day.⁵¹ Coruzzi and colleagues reported that potassium depletion increased BP and sodium sensitivity.⁵² In GenSalt Study, 60 mmol/day of potassium supplementation diminished BP increases due to high sodium intake.¹³ Dietary potassium deficiency induced sodium sensitivity by increasing renin-angiotensin-aldosterone activity and induction of tubulointerstitial injury.⁵³

Heritability of Sodium Sensitivity

Previous family studies conducted in various populations reported that the heritability of usual BP ranged from 20% to 50%.^{54,55} Furthermore, several studies reported moderate heritability of BP sodium sensitivity.^{56–58} Miller and colleagues studied 44 monozygotic twins and their families in a dietary sodium restriction (<75 mmol/day) intervention over a 12-week period.⁵⁶ The familial correlations for the BP responses to low-sodium as compared to baseline sodium intake were significant, and heritability of BP response was 54% for systolic and 34% for diastolic using the age-weight adjusted residual variance. Svetkey et al examined 20 African-American families selected through a hypertensive proband in whom sodium sensitivity was determined with an intravenous sodium-loading and furosemide volume-depletion protocol.⁵⁷ The heritability estimates based on familial correlations were 26% to 84% for mean arterial pressure, 26% to 74% for systolic, and 0.4% to 24% for diastolic BP responses to the sodium sensitivity maneuver, respectively.⁵⁷ In the GenSalt Study, the heritabilities for percentage of BP responses to low-sodium were 0.20, 0.21, and 0.23; and to high-sodium were 0.22, 0.33, and 0.33 for systolic, diastolic, and mean arterial pressure, respectively.⁵⁸ These findings suggest that BP responses to dietary sodium intervention are familial and genetic factors may play a moderate role in sodium sensitivity of BP.

Genetic Association Studies of Sodium Sensitivity

Candidate gene studies have provided evidence that genetic variants contribute to BP sodium sensitivity. Table 2 summarizes genetic variants related to sodium sensitivity of BP by biological pathways.

The renin-angiotensin-aldosterone system (RAAS)—Variants in several candidate genes in the RAAS pathway, including angiotensin-converting enzyme (*ACE*),^{59–61} angiotensinogen (*AGT*),^{62–67} cytochrome P450, family 11, subfamily B, polypeptide 2 (*CYP11B2*),^{68–70} and others^{71–75} have been associated with sodium sensitivity of BP.

In the GenSalt Study, the associations between twelve candidate genes in the RAAS (*ACE*, *ACE2*, *CYP11B1*, *CYP11B2*, *HSD11B1*, *HSD11B2*, *AGT*, *AGTR1*, *AGTR2*, *REN*, *NR3C2* and *RENB*) and sodium sensitivity of BP were examined.^{76, 77} Using a stringent significant threshold, six *ACE2* gene variants (rs1514283, rs1514282, rs4646176, rs2074192, rs714205, and rs2285666) were significantly associated with BP responses to low-sodium intervention. The first three of them were also significantly associated with mean arterial pressure response to high-sodium intervention. In addition, variants in *AGTR1* (rs4524238 and rs3772616), *HSD11B2* (rs5479), and *RENB* (rs1557501 and rs2269372) were significantly associated with BP responses to low-sodium intervention in single marker analyses and haplotype analyses.

Ion and water channels, transporters, and exchangers—Ion and water channels, transporters, and exchangers are actively involved in the regulation of sodium balance, blood volume, and BP. The renal epithelial sodium channel (*ENaC*) mediates sodium reabsorption in the renal tubule and plays a key role in sodium sensitivity of BP.^{78,79} A number of variants encoding *ENaC* subunits and other channels, transporters, and exchangers were identified as being related to sodium sensitivity of BP.^{80–87}

In the GenSalt Study, associations between genetic variants in *ENaC* and sodium sensitivity of BP were explored.^{89–91} Several variants in *SCNN1G* were significantly associated with BP response to a low-sodium intervention, including rs4073930, rs4073291, rs7404408, rs5735, rs4299163, and rs4499238. In addition, *SGK1* polymorphism rs2758151 was significantly associated with diastolic BP response to a high-sodium intervention. Furthermore, *SLC4A4* marker rs4254735 was significantly associated with diastolic BP response to a low-sodium intervention and rs10022637 was associated with systolic and diastolic BP responses to a high-sodium intervention.

In addition, two other studies reported that one *SLC8A1* SNP (rs434082) and three *WNK1* SNPs (rs880054, rs12828016, and rs2301880) were associated with sodium sensitivity in the Chinese population.^{92, 93}

Endothelial system—Endothelial dysfunction, especially the nitric oxide system, is involved in both hypertension and sodium sensitivity of BP.⁹⁴ Human studies have indicated that the increase in BP during sodium interventions was associated with the T-786C polymorphism of nitric oxide synthase gene.^{100, 101} Polymorphisms of other genes that play important roles in the pathogenesis of BP sodium sensitivity were also identified.^{95–99}

The GenSalt Study carefully examined fourteen candidate genes in the endothelial system and eleven NADPH oxidase-related genes.^{102,103} Variants in *DDAH1*, *COL18A1*, *VWF*, and *RAC1* genes were associated with BP sodium sensitivity. Interestingly enough, 10 variants from *SELE* displayed significant genotype-sex interactions, with 8 of them only significant in men.

Intracellular messengers—Both the guanine nucleotide-binding protein β -polypeptide 3 (*GNB3*) and α -adducin (*ADD1*) genes have been indicated in BP sodium sensitivity due to their biological effects on sodium homeostasis via sodium-proton exchanger activity and renal tubular sodium reabsorption, respectively.^{104–113} Many reports have investigated the association between the *GNB3* C825T and *ADD1* Gly460Trp polymorphisms and BP responses to sodium intervention. Although there is little evidence for a role of the *GNB3* C825T variant in sodium sensitivity, many studies have identified increased sodium sensitivity among those with the *ADD1* 460Trp allele compared to those with the 460Gly allele.^{106–113}

GenSalt investigators carefully genotyped variants covering the *GNB3* and *ADD1* genes.¹¹⁴ Non-significant associations were found regarding *GNB3* C825T polymorphism and the *ADD1* Gly460Trp polymorphism. Despite these negative results, a rare *ADD1* mutation, rs17833172, was identified to influence BP response to sodium interventions. Another novel finding is that participants carrying the A allele of SNP rs1129649 of the *GNB3* gene had a significantly decreased mean arterial pressure response to low-sodium intervention.

Sympathetic nervous system—One of the main mechanisms by which the sympathetic nervous system exerts its influence on BP is through its interaction with the kidney and the RAAS. Studies have demonstrated that increased renal sympathetic nerve activity results in renal vasoconstriction with decreased glomerular filtration rate and renal blood flow, increased renal vascular resistance, increased renal tubular reabsorption of sodium and water, and increased renal release of renin and norepinephrine.^{115,116} Several studies demonstrate that the genes encoding the G-protein-coupled receptor kinase type 4 (*GRK4*) and β -2 adrenergic receptor (*ADRB2*) are strong candidates for sodium sensitivity.^{64,117–119} One of the *ADRB2* variants, rs1042714, was successfully replicated in an independent Chinese population by Liu et al.⁹²

GNAI2 polymorphisms were found to be associated with hypertension risk in the Millennium Genome Project.¹²⁰ GenSalt investigators provided the first evidence that a *GNAI2* SNP (rs10510755) was positively associated with sodium sensitivity of BP.¹²¹ Further exploration of genes in this pathway could yield new insights into this trait.

Apelin-APJ system—The apelin system, including apelin and its G-protein coupled-receptor APJ, is a peptide signaling pathway that is implicated in the regulation of cardiovascular function and fluid homeostasis. This system is implicated in the regulation of BP via a NO/cGMP-dependent mechanism and can influence the Ca^{2+} transient in cardiomyocytes.¹²² Mutations of the apelin and APJ genes have recently been reported to be associated with hypertension.¹²³ SNPs rs2282623 and rs746886 in the apelin and APJ genes

were significantly associated with diastolic BP and mean arterial pressure responses to low-sodium intervention in the GenSalt Study population.⁷⁷

The natriuretic peptide system—Studies have demonstrated a role for the natriuretic peptide (*NPP*) system in the stimulation of diuresis and natriuresis via direct inhibition of sodium reabsorption in the medullary collecting duct, alteration of renal hemodynamics, and inhibition of renin and aldosterone activity.¹²⁴ Widecka *et al.* first identified an association between an atrial NPP (*NPPA*) variant and sodium sensitivity of BP.¹²⁵ In addition, Citterio *et al.* detected three SNPs in *PRKG1* gene (rs1904694, rs7905063 and rs7897633) that were associated with BP change after acute salt load.⁸²

The GenSalt study successfully replicated the *NPPA* variant, rs5063, in the Chinese population and a novel NPPC variant, rs2077386, was also identified.¹²⁶ In addition, the chromosomal region 2p24.3–2p24.1 was linked to BP responses to a high-sodium intervention.¹²⁷ The SNP rs16983422, upstream from *VSNL1* in the linkage region, had a marginally significant association with diastolic BP and mean arterial pressure responses to a high-sodium intervention.

The kallikrein-kinin system—Kinins are small peptides which are produced from kallikrein and cause vasodilation, diuresis, and natriuresis. The GenSalt Study systematically examined the associations of the eleven genes in KKS system (*KNG1*, *KLK1*, *KLKB1*, *BDKRB1*, *BDKRB2*, *SERPINA4*, *CPN1*, *CPN2*, *CPM*, *ECE1*, and *MME*) and sodium sensitivity of BP.¹²⁸ The *BDKRB2* variant, rs11847625, was significantly linked with sodium sensitivity and the carrying minor C allele could attribute to increased systolic BP response. Seven *ECE1* variants showed significant associations with increased diastolic BP response to low-sodium intervention. These seven SNPs were highly correlated with each other and haplotype analysis revealed a similar relationship.

Variants in other biological candidate genes have also been reported to associate with sodium sensitivity of blood pressure (Table 2).^{96,98,129–137}

Genome-wide Association Studies of Sodium Sensitivity

Genome-wide association study (GWAS) represents a powerful tool for investigating the common genetic variants associated with complex diseases. The GenSalt Study published the only GWAS findings on BP sodium sensitivity phenotypes and identified four novel loci for which physically mapped in or near *PRMT6* (rs1330225), *CDCA7* (rs10930597), *PIBF1* (rs8002688), and *IRAK1BP1* (rs16890334).¹³⁸ The most significant SNP from each of the first 2 loci is located in the intergenic regions. The *PIBF1* gene encodes a progesterone-induced molecule known to interact with leptin to mediate the effects of progesterone during pregnancy and the putative role of this gene in BP regulation is unclear. *IRAK1BP1* is part of the signaling pathway that leads to activation of nuclear factor- κ B.¹³⁹ A transcription factor for pro-inflammatory pathway genes, inhibition of nuclear factor- κ B, has been shown to decrease inflammation, BP, and angiotensin-II-induced target end-organ damage in animal models,¹⁴⁰ representing a plausible biological mechanism underlying the observed association. In addition, the nearby gene *PHIP* has been shown to modulate insulin

signaling, whereas *HMGN3* represents an important regulator of glucose-stimulated insulin secretion.¹³⁸

Sequencing Studies of Sodium Sensitivity

With the ability to directly identify causal variants and rare mutations, next-generation sequencing is becoming the primary discovery tool in genomic research.¹⁴¹ In the GenSalt Study, seven RAAS genes were re-sequenced using capillary-based sequencing methods.¹⁴² Aggregate rare variant analysis revealed an association of the RAAS pathway with BP sodium sensitivity. Carriers of rare RAAS variants had a 1.55-fold higher odds of sodium sensitivity compared to non-carriers ($P=0.004$). In addition, the *APLN* gene was significantly associated with sodium sensitivity, with rare *APLN* variants conferring a 2.22-fold higher odds of sodium sensitivity ($P=0.03$). Furthermore, a low-frequency, missense *RENBP* variant (rs78377269) was identified and each minor allele conferred a 2.21-fold increased odds of sodium sensitivity ($P=0.03$).¹⁴²

The GenSalt Study also re-sequenced three ENaC genes (*SCNN1A*, *SCNN1B*, and *SCNN1G*).¹⁴³ Carriers of *SCNN1A* rare variants had a 0.52 decreased odds of BP sodium sensitivity compared with non-carriers. In single-marker analyses, 3 independent common variants in *SCNN1A*, rs11614164, rs4764586, and rs3741914 were associated with sodium sensitivity ($P=4.4\times10^{-4}$, 1.1×10^{-8} , and 1.3×10^{-3}). Each copy of the minor allele of rs4764586 was associated with a 1.36-fold increased odds of sodium sensitivity, whereas each copy of the minor allele of rs11614164 and rs3741914 was associated with 0.68-fold and 0.69-fold decreased odds of sodium sensitivity, respectively.¹⁴³

Conclusion

Sodium sensitivity of BP is a common and reproducible phenotype which is not only associated with hypertension but also independently associated with cardiovascular disease and mortality. Age, gender, race/ethnicity, and baseline BP levels are important determinants of sodium sensitivity. Lifestyle (diet, alcohol, and physical activity) and genetic factors play important roles in determining individuals' sensitivity to sodium intake. Many genetic variants associated with sodium sensitivity of BP have been identified and contribute to understanding the etiology of hypertension. Despite remarkable progress, many questions related to sodium sensitivity of BP remain unclear. Future studies are warranted to better characterize sodium sensitivity in populations and to identify novel biological pathways and genetic determinants for sodium sensitivity. A better understanding of the genetic and environmental determinants of sodium sensitivity will help identify individuals at high risk for hypertension and who should receive a low sodium dietary intervention. In addition, identifying genes that interact significantly with dietary sodium intake on the regulation of BP will greatly contribute to the knowledge and underlying mechanisms of hypertension and help develop novel treatment for elevated BP.

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Figure 1.
GenSalt intervention program

Figure 2. Distribution of systolic (upper panels) and diastolic (low panels) BP responses to low-salt intervention (left panels) and high-salt intervention (right panels).

BP response to low-sodium = BP on low-sodium diet – BP at baseline and BP response to high-sodium = BP on high-sodium diet – BP on low-sodium diet. Adopted from reference 13.

Table 1.
Frequency of sodium sensitivity of blood pressure in hypertensives and normotensives

Authors	Definition	Proportion
Kawasaki ¹⁸	MAP 10% in sodium intake from 9 mmol (7 days) to 249 mmol/day (7 days)	47% in 12 hypertensives
Fujita ¹⁶	MAP 10% in sodium intake from 9 mmol (7 days) to 249 mmol/day (7 days)	50% in 18 hypertensives
Takeshita ¹⁷	MAP 10% in sodium intake from 70 mmol (7 days) to 345 mmol/day (7 days)	47% in 17 hypertensives
Campese ¹⁸	MAP 10% in sodium intake from 10 mmol (7 days) to 200 mmol/day (7 days)	60% in 20 hypertensives and 0% in 10 normotensives
Koolen ¹⁹	MAP 10 mm Hg in sodium intake from 50 mmol (14 days) to 300 mmol/day (14 days)	32% in 25 hypertensives
Sharma ¹⁴	MAP 3% in sodium intake from 20 mmol (7 days) to 220 mmol/day (7 days)	46% in 15 hypertensives
Morris ²⁰	MAP 3 mm Hg in sodium intake from 15 mmol (14 days) to 250 mmol/day (14 days)	79% in 24 normotensive blacks, 36% in 14 normotensive whites
Wright ²¹	MAP 10 mm Hg in sodium intake from <20 mmol (7 days) to >200 mmol/day (7 days)	42.9% in 49 normotensive blacks 50.0% in 52 normotensive whites 64.0% in 50 hypertensive blacks 52.1% in 48 hypertensive whites
He ¹³	MAP 5 mm Hg in sodium intake from 51.3 mmol (7 days) to 307.8 mmol (7 days)	46.7% of 105 in hypertensive males 53.9% of 76 in hypertensive females 27.2% of 883 in normotensive males 34.2% of 796 in normotensive females

MAP = mean arterial blood pressure

Table 2. Genes reported to associated with blood pressure salt sensitivity according to biological pathway

Gene symbol	Gene	Chr	Physical position (bp)	Significant SNPs
Renin-angiotensin-aldosterone system				
ACE ^{59,61}	Angiotensin-converting enzyme	17	61554422–61575741	I/D
ACE2 ⁷⁶	Angiotensin I converting enzyme 2	X	15561033–15602069	rs1514283; rs1514282; rs2074192; rs714205; rs4646176; rs2285666;
ADIPOQ ⁷⁹	Adiponectin, C1Q and collagen domain containing	3	186842690–186858463	rs16861205; rs822394;
AGT ^{92,67}	Angiotensinogen	1	230838269–230850336	rs5050; rs5051; rs699
AGTR1 ⁷⁷	Angiotensin II receptor, type 1	3	148697784–148743003	rs4524238; rs2638360; rs3772616; rs931490
AGTR2 ⁷¹	Angiotensin II receptor, type 2	X	115301958–115306225	rs11091046
CYP11B1 ^{4,72}	Cytochrome P450, family 11, subfamily B, polypeptide 1	8	143953773–143961236	NA
CYP11B2 ^{68–70}	Aldosterone synthase	8	143991975–143999259	rs1799998; intron 2 conversion
HSD11B2 ^{60,73,75,77}	Hydroxysteroid (11-beta) dehydrogenase type 2	16	67431117–67437553	rs5479; rs45483293; rs45598932; rs56057545; CA repeat
IRAK1BP1 ¹²⁹	Interleukin 1 receptor associated kinase 1 binding protein 1	6	78867472–78903102	rs16890334
RENBP ^{77,133}	Renin-binding protein	X	153935263–153944691	rs78377269; rs1557501; rs2071128; rs2269372; rs3027869
Ion and water channels, transporters, and exchangers				
AQP5 ⁸⁰	Aquaporin 5	12	50355279–50359461	–1364A/C ^b
CLCNKA ⁸¹	Chloride channel Ka	1	16348486–16360545	rs1010069; rs1739843; rs1805152; rs848307
SCN1A ¹³⁴	Epithelial sodium channel alpha subunit	12	6346847–6375549	rs4764586; rs3741914; rs11614164;
SCNN1G ⁸⁹	Epithelial sodium channel gamma subunit	16	23182715–23216883	rs4073291; rs4499238; rs4073930; rs4299163; rs5735; rs7404408
SGK1 ^{87,90}	Serum/glucocorticoid regulated kinase 1	6	134169252–134174896	rs2758151; rs9402571
SLC24A3 ⁸²	Solute carrier family 24 member 3	20	9193290–19703541	rs3790261; rs6112470
SLC4A4 ⁹¹	Solute carrier family 4 member 4	4	71187286–71569717	rs4254735; rs10022637
SLC4A5 ⁸⁶	Solute carrier family 4 member 5	2	74221467–74343409	rs7571842; rs10177833
SLC8A1 ^{82,92}	Solute carrier family 8 member A1	2	40115031–40512361	rs11893826; rs434082
WNK1 ^{83–85,93}	WNK lysine deficient protein kinase 1	12	752923–911452	rs2301880; rs880054; rs2286007; rs956868; rs12828016; rs2255390; 27bp VNTR
Endothelial system				

Gene symbol	Gene	Chr	Physical position (bp)	Significant SNPs
COL18A1 ¹⁰²	Collagen type XVIII alpha 1 chain	21	45455531–45513719	rs2838944
CYBA ⁹⁵	Cytochrome b-245, a-polypeptide	16	88709697–88717457	rs4673
DDAH1 ¹⁰²	Dimethylarginine Dimethylaminohydrolase 1	1	85318486–85465144	rs111161637
EDN1 ²⁹⁶	Endothelin 1	6	12290529–12297427	NA
EDNRB ⁹⁷	Endothelin receptor type b	13	78469616–78493903	G1065A ^b
ATP2B1 ⁹⁸	ATPase, Ca ⁺⁺ transporting, plasma membrane 1	12	89,588,072–89,708,831	rs2681472
ESR1 ³⁰	Estrogen receptor 1	6	151690496–152103274	rs9340844; rs9397453; rs9371562; rs9397459; rs9383951
ESR2 ⁹⁹	Estrogen receptor 2	14	64,233,088–64,294,360	rs10144225
NOS3 ^{100,101}	Nitric oxide synthase 3	7	150688144–150711687	rs2070744
RAC1 ¹⁰³	Rac family small GTPase 1	7	6374523–6403977	rs6967221
SELE ¹⁰²	Selectin E	1	169722641–169734062	rs5356; rs3917430; rs3917428; rs5368; rs3917436; rs3917423; rs3917406; rs932307; rs1534904; rs3917412
VWF ¹⁰²	Von Willebrand factor	12	5948874–6124675	rs2239153
Intracellular messengers				
ADD1 ^{83,106–114}	Alpha-adducin	4	2843857–2930073	rs17833172; rs4961
GNB3 ¹¹⁴	Guanine nucleotide binding protein (G protein) beta-polypeptide 3	12	6840211–6847393	rs1129649;
Sympathetic nervous system				
ADRB2 ^{64,117,118}	Adrenoceptor beta 2	5	148825245–148828687	rs1042714; rs1042713
GNAI2 ¹²¹	G protein subunit alpha 12	3	50235952–50259355	rs10510755
GRK4 ^{88,119}	G-protein-coupled receptor kinase 4	4	2965343–3042474	rs1801058; rs2960306
Apelin-APJ system				
APLNR ⁷⁶	Apelin receptor	11	57233593–57237314	rs2282623; rs721608; rs746886
Natriuretic peptide system				
NPPA ^{125,126}	Natriuretic peptide A	1	11845709–11847783	rs5063
NPPC ¹²⁶	Natriuretic peptide C	2	231921820–231926403	rs2077386
PRKG1 ⁸²	cGMP-dependent protein kinase 1	10	50991358–52298350	rs7897633; rs1904694; rs7905063
VSNL1 ¹²⁷	Visinin like 1	2	17539126–17655528	rs16983422
Kallikrein-kinin system				

Gene symbol	Gene	Chr	Physical position (bp)	Significant SNPs
BDKRB2 ¹²⁸	Bradykinin receptor B2	14	96204795–96244164	rs11847625
ECE1 ¹²⁸	Endothelin converting enzyme 1	1	21219859–21290489	rs213011; rs169884; rs84853; rs213012; rs213014; rs213018; rs213025
KLKI ⁶⁴	Kalikrein 1	19	51322404–51327043	rs5516
Others				
BCAT1 ⁹⁸	Branched chain aminotransferase 1	12	24810022–24949459	rs7961152
ABCB1 ¹²⁹	ATP-binding cassette, subfamily B (MDR/TAP), member 1	7	87133179–87342639	rs1045642
CYP3A5 ^{129–131}	Cytochrome P450, family 3, subfamily A, polypeptide 5	7	99245813–99277621	CYP3A5*1 ^b
DYNLT1 ^{d,132}	Dynein, light chain, Tctex-type 1	6	159057506–159065804	NA
FAH ^{d,132}	Fumarylacetoacetate hydrolase	15	80445233–80478924	NA
FAM84A ¹²⁷	Family with sequence similarity 84 member A	2	14632686–14640046	rs11674786
FGF5 ⁹⁸	Fibroblast growth factor 5	4	80266599–80290194	rs16998073
HNRNPK ^{d,133}	Heterogeneous nuclear ribonucleoprotein K	9	86582998–86595569	NA
HP1 ³⁴	Haptoglobin	16	72088508–72094955	Hpl ^b
LOC100132798 ⁹⁸	NA	NA	NA	rs2398162
LSR ^{d,132}	Lypolysis stimulated lipoprotein receptor	19	35739559–35758867	NA
MYADM ^{d,132}	Myeloid-associated differentiation marker	19	54369611–54379689	NA
NEDD4L ⁹⁶	Neural precursor cell expressed, developmentally down-regulated 4-like	18	55711619–56068772	rs4149601
NOS1 ^{d,135}	Neuronal nitric oxide synthase	12	117645947–117799607	NA
SERPINH1 ^{d,132}	Serpin peptidase inhibitor, clade H (heat shock protein 47), member 1	11	75273101–75283849	NA
STK39 ^{98,136}	Serine threonine kinase 39	2	168810530–169104105	rs359296007; rs3754777; rs6749447
STRN ¹³⁷	Striatin	2	36843640–36966472	rs2540923

bp, base pair; Chr, chromosome; I/D, insertion/deletion polymorphism; NA, not applicable

^aFindings exclusively from studies of animal models.