Journal of Human Hypertension (2020) 34:94–107
https://doi.org/10.1038/s41371-018-0152-0

REVIEW ARTICLE

Sodium sensitivity of blood pressure in Chinese populations

Yang Liu[1,2] · Mengyao Shi[2] · Jacquelyn Dolan[2,3] · Jiang He[2]

Received: 25 September 2018 / Revised: 15 November 2018 / Accepted: 6 December 2018 / Published online: 10 January 2019

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 ~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 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 [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.

✉ Jiang He
jhe@tulane.edu

[1] Department of Cardiology, The First Affiliated Hospital of Soochow University, Suzhou, China

[2] Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA

[3] Louisiana State University School of Allied Health Professions, New Orleans, LA, USA

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 mmHg) 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 1–2 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 (Fig. 1) [13]. Study participants received a low-sodium diet (3 g of sodium chloride or 51.3 mmol of sodium per day) for 7 days, followed by a high-sodium diet (18 g 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.

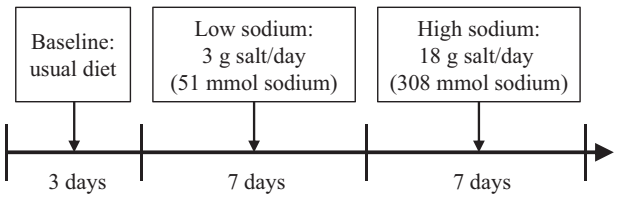

Fig. 1 GenSalt intervention program

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 h 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 h). BP was measured again in the following morning. Sodium sensitivity of BP was defined as a decrease in mean arterial pressure ≥ 10 mmHg, and salt resistance was defined as a decrease < 6 mmHg [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

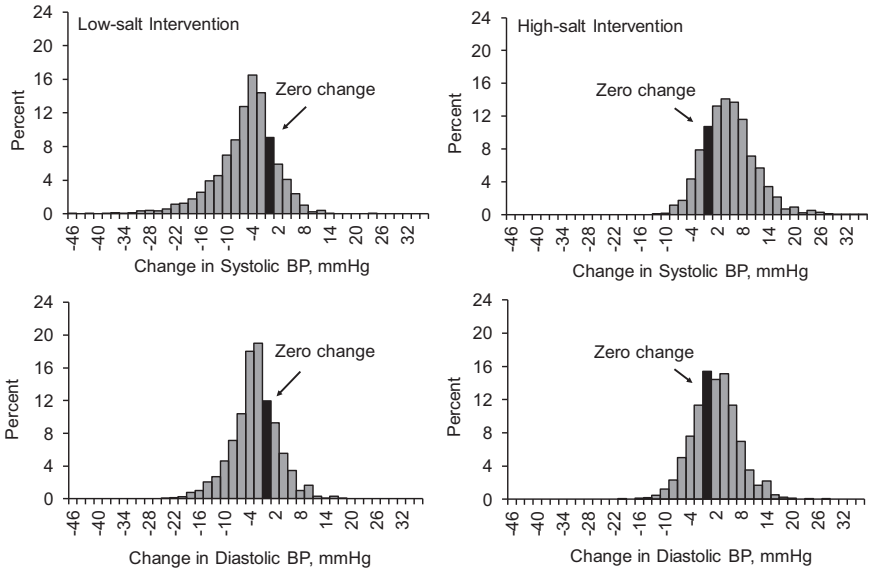

Fig. 2 Distribution of systolic (upper panels) and diastolic (low panels) BP responses to low-salt intervention (left panels) and high-salt intervention (right panels). BP response to low-sodium = BP on low-sodium diet—BP at baseline and BP response to high-sodium = BP on high-sodium diet—BP on low-sodium diet. Adopted from ref. [13]

of BP responses to low and high dietary sodium interventions from the GenSalt Study are shown in Fig. 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 [1, 8, 16, 17]. 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 [18]. In addition, sodium sensitivity was defined as the difference in mean arterial pressure between low and high-sodium interventions ≥ 10% or ≥10 mmHg in some studies [8, 16–20] or ≥3% or ≥3 mmHg in others [14, 21]. Using a definition of mean arterial pressure ≥ 10% or ≥10 mmHg, the proportions of sodium sensitivity varied from 32% to 64% among individuals with hypertension and 0–50% among individuals with normal BP [19, 20].

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 mmHg 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 mmHg 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 [20, 31]. In the DASH-sodium trials, the decrease in BP associated with reduced sodium intake was more pronounced in normotensive African Americans [31].

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

Authors	Definition	Proportion
Kawasaki [8]	ΔMAP ≥ 10% in sodium intake from 9 mmol (7 days) to 249 mmol/day (7 days)	47% in 12 hypertensives
Fujita [16]	ΔMAP ≥ 10% in sodium intake from 9 mmol (7 days) to 249 mmol/day (7 days)	50% in 18 hypertensives
Takeshita [18]	ΔMAP ≥ 10% in sodium intake from 70 mmol (7 days) to 345 mmol/day (7 days)	47% in 17 hypertensives
Campese [19]	ΔMAP ≥ 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 [17]	ΔMAP ≥ 10 mmHg in sodium intake from 50 mmol (14 days) to 300 mmol/day (14 days)	32% in 25 hypertensives
Sharma [14]	ΔMAP ≥ 3% in sodium intake from 20 mmol (7 days) to 220 mmol/day (7 days)	46% in 15 hypertensives
Morris [21]	ΔMAP ≥ 3 mmHg 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 [20]	ΔMAP ≥ 10 mmHg 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]	ΔMAP ≥ 5 mmHg 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

Wright et al. reported the prevalence of sodium sensitivity was similar in both black and white normotensives but increased in African Americans hypertensives [20]. The reason for this difference in race may be because blacks have an intrinsic reduction in the ability to excrete sodium compared with whites [32].

Determinations of sodium sensitivity

Usual BP levels

Individuals with hypertension have a greater BP response to changes in sodium intake than individuals without hypertension [9, 13, 20]. 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 mmHg ($P < 0.0001$ 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 mmHg during low-sodium intervention and 4.1, 4.4, 4.4, and 6.3 mmHg 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 [38, 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 mmHg) than non-obese adolescents (1 mmHg) after successive 2-week periods of a high-salt diet (>250 mmol of sodium per day) and a low-salt diet (<30 mmol per day)

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 [58–60]	Angiotensin-converting enzyme	17	61,554,422–61,575,741	I/D
ACE2 [75]	Angiotensin I converting enzyme 2	X	15,561,033–15,602,069	rs1514283; rs1514282; rs2074192; rs714205; rs4646176; rs2285666;
ADIPOQ [143]	Adiponectin, C1Q and collagen domain containing	3	186,842,690–186,858,463	rs16861205; rs822394;
AGT [61–66]	Angiotensinogen	1	230,838,269–230,850,336	rs5050; rs5051; rs699
AGTR1 [76]	Angiotensin II receptor, type 1	3	1,48,697,784–1,48,743,003	rs4524238; rs2638360; rs3772616; rs931490
AGTR2 [70]	Angiotensin II receptor, type 2	X	115,301,958–115,306,225	rs11091046
CYP11B1[a][71]	Cytochrome P450, family 11, subfamily B, polypeptide 1	8	143,953,773–143,961,236	NA
CYP11B2 [67–69]	Aldosterone synthase	8	143,991,975–143,999,259	rs1799998; intron 2 conversion
HSD11B2 [59, 72–74, 76]	Hydroxysteroid (11-beta) dehydrogenase type 2	16	67,431,117–67,437,553	rs5479; rs45483293; rs45598932; rs56057545; CA repeat
IRAK1BP1 [136]	Interleukin 1 receptor associated kinase 1 binding protein 1	6	78,867,472–78,903,102	rs16890334
RENBP [76, 140]	Renin-binding protein	X	153,935,263–153,944,691	rs78377269; rs1557501; rs2071128; rs2269372; rs3027869
Ion and water channels, transporters, and exchangers				
AQP5 [79]	Aquaporin 5	12	50,355,279–50,359,461	−1364A/C[b]
CLCNKA [80]	Chloride channel Ka	1	16,348,486–16,360,545	rs1010069; rs1739843; rs1805152; rs848307
SCNN1A [141]	Epithelial sodium channel alpha subunit	12	6,346,847–6,375,549	rs4764586; rs3741914; rs11614164;
SCNN1G [87]	Epithelial sodium channel gamma subunit	16	23,182,715–23,216,883	rs4073291; rs4499238; rs4073930; rs4299163; rs5735; rs7404408
SGK1 [86, 88]	Serum/glucocorticoid regulated kinase 1	6	134,169,252–134,174,896	rs2758151; rs9402571
SLC24A3 [81]	Solute carrier family 24 member 3	20	9,193,290–19,703,541	rs3790261; rs6112470
SLC4A4 [89]	Solute carrier family 4 member 4	4	71,187,286–71,569,717	rs4254735; rs10022637
SLC4A5 [85]	Solute carrier family 4 member 5	2	74,221,467–74,343,409	rs7571842; rs10177833
SLC8A1 [81, 90]	Solute carrier family 8 member A1	2	40,115,031–40,512,361	rs11893826; rs434082
WNK1 [82–84, 91]	WNK lysine deficient protein kinase 1	12	752,923–911,452	rs2301880; rs880054; rs2286007; rs956868; rs12828016; rs2255390; 27 bp VNTR
Endothelial system				
COL18A1 [100]	Collagen type XVIII alpha 1 chain	21	45,455,531–45,513,719	rs2838944
CYBA [95]	Cytochrome b-245, a-polypeptide	16	88,709,697–88,717,457	rs4673
DDAH1 [100]	Dimethylarginine Dimethylaminohydrolase 1	1	85,318,486–85,465,144	rs11161637
EDN1[a][96]	Endothelin 1	6	12,290,529–12,297,427	NA
EDNRB [97]	Endothelin receptor type b	13	78,469,616–78,493,903	G1065A[b]
ATP2B1 [98]	ATPase, Ca^{2+} transporting, plasma membrane 1	12	89,588,072–89,708,831	rs2681472
ESR1 [30]	Estrogen receptor 1	6	151,690,496–152,103,274	rs9340844; rs9397453; rs9371562; rs9397459; rs9383951
ESR2 [99]	Estrogen receptor 2	14	64,233,088–64,294,360	rs10144225
NOS3 [93, 94]	Nitric oxide synthase 3	7	150,688,144–150,711,687	rs2070744
RAC1 [101]	Rac family small GTPase 1	7	6,374,523–6,403,977	rs6967221
SELE [100]	Selectin E	1	169,722,641–169,734,062	rs5356; rs3917430; rs3917428; rs5368; rs3917436; rs3917423; rs3917406; rs932307; rs1534904; rs3917412

Table 2 (continued)

Gene symbol	Gene	Chr	Physical position (bp)	Significant SNPs
VWF [100]	Von Willebrand factor	12	5,948,874–6,124,675	rs2239153
Intracellular messengers				
ADD1 [82, 104–112]	Alpha-adducin	4	2,843,857–2,930,073	rs17833172; rs4961
GNB3 [112]	Guanine nucleotide-binding protein (G protein) beta-polypeptide 3	12	6,840,211–6,847,393	rs1129649
Sympathetic nervous system				
ADRB2 [63, 115, 116]	Adrenoceptor beta 2	5	148,825,245–148,828,687	rs1042714; rs1042713
GNAI2 [119]	G protein subunit alpha i2	3	50,235,952–50,259,355	rs10510755
GRK4 [117, 142]	G-protein-coupled receptor kinase 4	4	2,965,343–3,042,474	rs1801058; rs2960306
Apelin–APJ system				
APLNR [75]	Apelin receptor	11	57,233,593–57,237,314	rs2282623; rs721608; rs746886
Natriuretic peptide system				
NPPA [123, 124]	Natriuretic peptide A	1	11,845,709–11,847,783	rs5063
NPPC [124]	Natriuretic peptide C	2	231,921,820–231,926,403	rs2077386
PRKG1 [81]	cGMP-dependent protein kinase 1	10	50,991,358–52,298,350	rs7897633; rs1904694; rs7905063
VSNL1 [125]	Visinin like 1	2	17,539,126–17,655,528	rs16983422
Kallikrein–kinin system				
BDKRB2 [126]	Bradykinin receptor B2	14	96,204,795–96,244,164	rs11847625
ECE1 [126]	Endothelin converting enzyme 1	1	21,219,859–21,290,489	rs213011; rs169884; rs84853; rs213012; rs213014; rs213018; rs213025
KLK1 [63]	Kalikrein 1	19	51,322,404–51,327,043	rs5516
Others				
BCAT1 [98]	Branched chain aminotransferase 1	12	24,810,022–24,949,459	rs7961152
ABCB1 [127]	ATP-binding cassette, subfamily B (MDR/TAP), member 1	7	87,133,179–87,342,639	rs1045642
CYP3A5 [127–129]	Cytochrome P450, family 3, subfamily A, polypeptide 5	7	99,245,813–99,277,621	CYP3A5*1[b]
DYNLT1[a][130]	Dynein, light chain, Tctex-type 1	6	159,057,506–159,065,804	NA
FAH[a,132]	Fumarylacetoacetate hydrolase	15	80,445,233–80,478,924	NA
FAM84A [125]	Family with sequence similarity 84 member A	2	14,632,686–14,640,046	rs11674786
FGF5 [98]	Fibroblast growth factor 5	4	80266599–80290194	rs16998073
HNRNPK[a][131]	Heterogeneous nuclear ribonecleoprotein K	9	86,582,998–86,595,569	NA
HP [132]	Haptoglobin	16	72,088,508–72,094,955	Hp1[b]
LOC100132798 [98]	NA	NA	NA	rs2398162
LSR[a][130]	Lypolysis stimultated lipoprotein receptor	19	35,739,559–35,758,867	NA
MYADM[a][130]	Myeloid-associated differentiation marker	19	54,369,611–54,379,689	NA
NEDD4L [96]	Neural precursor cell expressed, developmentally down-regulated 4-like	18	55,711,619–56,068,772	rs4149601
NOS1[a][133]	Neuronal nitric oxide synthase	12	117,645,947–117,799,607	NA
SERPINH1[a][130]	Serpin peptidase inhibitor, clade H (heat shock protein 47), member 1	11	75,273,101–75,283,849	NA
STK39 [98, 134]	Serine threonine kinase 39	2	168,810,530–169,104,105	rs35929607; rs3754777; rs6749447
STRN [135]	Striatin	2	36,843,640–36,966,472	rs2540923

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

[a]Findings exclusively from studies of animal models

[b]rs number could not be identified

[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 –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 hypertension [47] 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 [21, 51]. 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 [21]. Coruzzi and colleagues reported that potassium depletion increased BP and sodium sensitivity [51]. 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 [52].

Heritability of sodium sensitivity

Previous family studies conducted in various populations reported that the heritability of usual BP ranged from 20% to 50% [53, 54]. Furthermore, several studies reported moderate heritability of BP sodium sensitivity [55–57]. Miller and colleagues studied 44 monozygotic twins and their families in a dietary sodium restriction (<75 mmol/day) intervention over a 12-week period [55]. 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 [56]. The heritability estimates based on familial correlations were 26–84% for mean arterial pressure, 26–74% for systolic, and 0.4–24% for diastolic BP responses to the sodium sensitivity maneuver, respectively [56]. 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 [57]. 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*) [58–60], angiotensinogen (*AGT*) [61–66], cytochrome P450, family 11, subfamily B, polypeptide 2 (*CYP11B2*) [67–69], and others [70–74] have been associated with sodium sensitivity of BP.

In the GenSalt Study, the associations between 12 candidate genes in the RAAS (*ACE, ACE2, CYP11B1, CYP11B2, HSD11B1, HSD11B2, AGT, AGTR1, AGTR2, REN, NR3C2*, and *RENBP*) and sodium sensitivity of BP were examined [75, 76]. 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 *RENBP* (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 [77, 78]. A number of variants encoding *ENaC* subunits and other channels, transporters, and exchangers were identified as being related to sodium sensitivity of BP [79–86].

In the GenSalt Study, associations between genetic variants in *ENaC* and sodium sensitivity of BP were explored [87–89]. 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 [90, 91].

Endothelial system

Endothelial dysfunction, especially the nitric oxide system, is involved in both hypertension and sodium sensitivity of BP [92]. Human studies have indicated that the increase in BP during sodium interventions was associated with the T-786C polymorphism of nitric oxide synthase gene [93, 94]. 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 14 candidate genes in the endothelial system and 11 NADPH oxidase-related genes [100, 101]. 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 eight of them only significant in men.

Intracellular messengers

Both the guanine nucleotide-binding protein β-polypeptide 3 (*GNB3*) and a-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 [102–111]. 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 [104–111].

GenSalt investigators carefully genotyped variants covering the *GNB3* and *ADD1* genes [112]. 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 [113, 114]. 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 [63, 115–117]. One of the *ADRB2* variants, rs1042714, was successfully replicated in an independent Chinese population by Liu et al. [90].

GNAI2 polymorphisms were found to be associated with hypertension risk in the Millennium Genome Project [118]. GenSalt investigators provided the first evidence that a *GNAI2* SNP (rs10510755) was positively associated with sodium sensitivity of BP [119]. 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 [120]. Mutations of the apelin and APJ genes have recently been reported to be associated with hypertension [121]. 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 [76].

The natriuretic peptide (NPP) system

Studies have demonstrated a role for the *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 [122]. Widecka et al. first identified an association between an atrial NPP (*NPPA*) variant and sodium sensitivity of BP [123]. 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 [81].

The GenSalt study successfully replicated the *NPPA* variant, rs5063, in the Chinese population and a novel *NPPC* variant, rs2077386, was also identified [124]. In addition, the chromosomal region 2p24.3-2p24.1 was linked to BP responses to a high-sodium intervention [125]. 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 11 genes in KKS system (*KNG1*, *KLK1*, *KLKB1*, *BDKRB1*, *BDKRB2*, *SERPINA4*, *CPN1*, *CPN2*, *CPM*, *ECE1*, and *MME*) and sodium sensitivity of BP [126]. 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 BP (Table 2) [96, 98, 127–135].

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) [136]. The most significant SNP from each of the first two 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-B1 [137]. A transcription factor for pro-inflammatory pathway genes, inhibition of nuclear factor-κB, has been shown to decrease inflammation, BP, and angiotensin-II-induced target end-organ damage in animal models [138], 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 [136].

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 [139]. In the GenSalt Study, seven RAAS genes were re-sequenced using capillary-based sequencing methods [140]. 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 ($P = 0.03$) [140].

The GenSalt Study also re-sequenced three ENaC genes (*SCNN1A*, *SCNN1B*, and *SCNN1G*) [141]. Carriers of *SCNN1A* rare variants had a 0.52 decreased odds of BP sodium sensitivity compared with non-carriers. In single-marker analyses, three independent common variants in *SCNN1A*, rs11614164, rs4764586, and rs3741914 were associated with sodium sensitivity ($P = 4.4 \times 10^{-4}$, 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 [141].

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.

Acknowledgements Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number P20GM109036. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. YL is supported by a research training grant (D43TW009107) from the National Institutes of Health John E. Fogarty International Center, Bethesda, Maryland.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Mills KT, Bundy JD, Kelly TN, Reed J, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016;134:441–50.
2. He J, Gu D, Chen J, Wu X, Kelly TN, Huang JF, et al. Premature deaths attributable to blood pressure in China: a prospective cohort study. Lancet. 2009;374:1765–72.
3. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet. 2008;371:1513–8.
4. He J, Tell GS, Tang YC, Mo PS, He GQ. Relation of electrolytes to blood pressure in men. The Yi people study. Hypertension. 1991;17:378–85.
5. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, et al. Intersalt revisited: further analyses of 24h sodium excretion and blood pressure within and across populations. BMJ. 1996;312:1249–53.
6. He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ. 2013;346:f1325 https://doi.org/10.1136/bmj.f1325
7. Newberry SJ, Chung M, Anderson CA, Chen C, Fu Z, Tang A, et al. Sodium and potassium intake: effects on chronic disease outcomes and risks. Comparative effectiveness review no. 206. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2015-00010-I.) AHRQ Publication No. 18-EHC009-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2018.
8. Kawasaki T, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. Am J Med. 1978;64:193–8.
9. Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension. 1996;27:481–90.
10. Frame AA, Wainford RD. Renal sodium handling and sodium sensitivity. Kidney Res Clin Pract. 2017;36:117–31.
11. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension. 2001;37:429–32.

12. Morimoto A, Uzu T, Fujii T, Nishimura M, Kuroda S, Nakamura S, et al. Sodium sensitivity and cardiovascular events in patients with essential hypertension. Lancet. 1997;350:1734–7.
13. He J, Gu D, Chen J, Jaquish CE, Rao DC, Hixson JE, et al. Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. J Hypertens. 2009;27:48–54.
14. Sharma AM, Schattenfroh S, Kribben A, Distler A. Reliability of salt-sensitivity testing in normotensive subjects. Klin Wochenschr. 1989;67:632–4.
15. Gu D, Zhao Q, Chen J, Chen JC, Huang J, Bazzano LA, et al. Reproducibility of blood pressure responses to dietary sodium and potassium interventions. The GenSalt study. Hypertension. 2013;62:499–505.
16. Fujita T. The effect of high-sodium intake and furosemide on blood pressure and other related variables in salt-sensitive hypertension. Jpn J Med. 1982;21:157–8.
17. Koolen MI, Bussemaker-Verduyn den Boer E, van Brummelen P. Clinical biochemical and haemodynamic correlates of sodium sensitivity in essential hypertension. J Hypertens Suppl. 1983;1:21–23.
18. Takeshita A, Imaizumi T, Ashihara T, Nakamura M. Characteristics of responses to salt loading and deprivation in hypertensive subjects. Circ Res. 1982;51:457–64.
19. Campese VM, Romoff MS, Levitan D, Saglikes Y, Friedler RM, Massry SG. Abnormal relationship between sodium-intake and sympathetic nervous-system activity in salt-sensitive patients with essential-hypertension. Kidney Int. 1982;21:371–8.
20. Wright JT Jr., Rahman M, Scarpa A, Fatholahi M, Griffin V, Jean-Baptiste R, et al. Determinants of salt sensitivity in black and white normotensive and hypertensive women. Hypertension. 2003;42:1087–92.
21. Morris RC Jr, Sebastian A, Forman A, Tanaka M, Schmidlin O. Normotensive salt sensitivity: effects of race and dietary potassium. Hypertension. 1999;33:18–23.
22. Weinberger MH, Fineberg NS. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. Hypertension. 1991;18:67–71.
23. Frame AA, Wainford RD. Mechanisms of altered renal sodium handling in age-related hypertension. Am J Physiol Ren Physiol. 2018;315:F1–F6.
24. Miller JZ, Weinberger MH, Daugherty SA, Fineberg NS, Christian JC, Grim CE. Heterogeneity of blood pressure response to dietary sodium restriction in normotensive adults. J Chronic Dis. 1987;40:245–50.
25. Hurwitz S, Fisher ND, Ferri C, Hopkins PN, Williams GH, Hollenberg NK. Controlled analysis of blood pressure sensitivity to sodium intake: interactions with hypertension type. J Hypertens. 2003;21:951–9.
26. Wilson DK, Bayer L, Sica DA. Variability in salt sensitivity classifications in black male versus female adolescents. Hypertension. 1996;28:250–5.
27. Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, et al. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. Ann Intern Med. 2001;135:1019–28.
28. Stachenfeld NS, Taylor HS. Effects of estrogen and progesterone administration on extracellular fluid. J Appl Physiol. 2004;96:1011–8.
29. Stachenfeld NS, DiPietro L, Palter SF, Nadel ER. Estrogen influences osmotic secretion of AVP and body water balance in postmenopausal women. Am J Physiol. 1998;274:R187–R195.
30. Kelly TN, Rebholz CM, Gu D, Hixson JE, Rice TK, Cao J, et al. Analysis of sex hormone genes reveals gender differences in the genetic etiology of blood pressure salt sensitivity: the GenSalt study. Am J Hypertens. 2013;26:191–200.
31. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344:3–10.
32. Luft FC, Rankin LI, Bloch R, Weyman AE, Willis LR, Murray RH, et al. Cardiovascular and humoral responses to extremes of sodium intake in normal black and white men. Circulation. 1979;60:697–706.
33. Godden JO, Roth GM, Hines EA, Schlegel JF. The changes in the intra-arterial pressure during immersion of the hand in ice-cold water. Circulation. 1955;12:963–73.
34. Victor RG, Leimbach WN Jr, Seals DR, Wallin BG, Mark AL. Effects of the cold pressor test on muscle sympathetic nerve activity in humans. Hypertension. 1987;9:429–36.
35. Kasagi F, Akahoshi M, Shimaoka K. Relation between cold pressor test and development of hypertension based on 28-year follow-up. Hypertension. 1995;25:71–76.
36. Strazzullo P, Strazzullo P, Barbato A, Vuotto P, Galletti F. Relationships between salt sensitivity of blood pressure and sympathetic nervous system activity: a short review of evidence. Clin Exp Hypertens. 2001;23:25–33.
37. Chen J, Gu D, Jaquish CE, Chen CS, Rao DC, Liu D, et al. Association between blood pressure responses to the cold pressor test and dietary sodium intervention in a Chinese population. Arch Intern Med. 2008;168:1740–6.
38. Zhao Q, Gu D, Chen J, Li J, Cao J, Lu F, et al. Blood pressure responses to dietary sodium and potassium interventions and the cold pressor test: the GenSalt replication study in rural North China. Am J Hypertens. 2014;27:72–80.
39. Zhao Q, Bazzano LA, Cao J, Li J, Chen J, Huang J. et al. Reproducibility of blood pressure response to the cold pressor test: the GenSalt Study. Am J Epidemiol. 2012;176(Suppl. 7): S91–98.
40. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, et al. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med. 1989;321:580–5.
41. Uzu T, Kimura G, Yamauchi A, Kanasaki M, Isshiki K, Araki SI, et al. Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. J Hypertens. 2006;24:1627–32.
42. Chen J, Gu D, Huang J, Rao DC, Jaquish CE, Hixson JE, et al. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: a dietary intervention study. Lancet. 2009;373:829–35.
43. Strazzullo P, Barba G, Cappuccio FP, Siani A, Trevisan M, Farinaro E, et al. Altered renal sodium handling in men with abdominal adiposity: a link to hypertension. J Hypertens. 2001;19:2157–64.
44. Hoffmann IS, Cubeddu LX. Increased blood pressure reactivity to dietary salt in patients with the metabolic syndrome. J Hum Hypertens. 2007;21:438–44.
45. Shimamoto K, Hirata A, Fukuoka M, Higashiura K, Miyazaki Y, Shiiki M, et al. Insulin sensitivity and the effects of insulin on renal sodium handling and pressor systems in essential hypertensive patients. Hypertension. 1994;23(1 Suppl):I29–33.
46. Nizar JM, Bhalla V. Molecular mechanisms of sodium-sensitive hypertension in the metabolic syndrome. Curr Hypertens Rep. 2017;19:60.
47. Carnethon MR, Evans NS, Church TS, Lewis CE, Schreiner PJ, Jacobs DR Jr, et al. Joint associations of physical activity and aerobic fitness on the development of incident hypertension: coronary artery risk development in young adults. Hypertension. 2010;56:49–55.

48. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2002;136:493–503.
49. Rebholz CM, Gu D, Chen J, Huang JF, Cao J, Chen JC, et al. Physical activity reduces salt sensitivity of blood pressure: the Genetic Epidemiology Network of Salt Sensitivity Study. Am J Epidemiol. 2012;176(Suppl. 7):S106–113.
50. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA. 1997;277:1624–32.
51. Coruzzi P, Brambilla L, Brambilla V, Gualerzi M, Rossi M, Parati G, et al. Potassium depletion and salt sensitivity in essential hypertension. J Clin Endocrinol Metab. 2001;86:2857–62.
52. Ray PE, Suga S, Liu XH, Huang X, Johnson RJ. Chronic potassium depletion induces renal injury, salt sensitivity, and hypertension in young rats. Kidney Int. 2001;59:1850–8.
53. Rotimi CN, Cooper RS, Cao G, Ogunbiyi O, Ladipo M, Owoaje E, et al. Maximum-likelihood generalized heritability estimate for blood pressure in Nigerian families. Hypertension. 1999;33:874–8.
54. Mitchell GF, DeStefano AL, Larson MG, Benjamin EJ, Chen MH, Vasan RS, et al. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham Heart Study. Circulation. 2005;112:194–9.
55. Miller JZ, Weinberger MH, Christian JC, Daugherty SA. Familial resemblance in the blood pressure response to sodium restriction. Am J Epidemiol. 1987;126:822–30.
56. Svetkey LP, McKeown SP, Wilson AF. Heritability of salt sensitivity in black Americans. Hypertension. 1996;28:854–8.
57. Gu D, Rice T, Wang S, Yang W, Gu C, Chen CS, et al. Heritability of blood pressure responses to dietary sodium and potassium intake in a Chinese population. Hypertension. 2007;50:116–22.
58. Dengel DR, Brown MD, Ferrell RE, Supiano MA. Role of angiotensin converting enzyme genotype in sodium sensitivity in older hypertensives. Am J Hypertens. 2001;14:1178–84.
59. Poch E, Gonzalez D, Giner V, Bragulat E, Coca A, de La, Sierra A. Molecular basis of salt sensitivity in human hypertension: evaluation of renin-angiotensin-aldosterone system gene polymorphisms. Hypertension. 2001;38:1204–9.
60. Hiraga H, Oshima T, Watanabe M, Ishida M, Ishida T, Shingu T, et al. Angiotensin I-converting enzyme gene polymorphism and salt sensitivity in essential hypertension. Hypertension. 1996;27:569–72.
61. Johnson AG, Nguyen TV, Davis D. Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects. J Hypertens. 2001;19:1053–60.
62. Schorr U, Blaschke K, Beige J, Distler A, Sharma AM. Angiotensinogen M235T variant and salt sensitivity in young normotensive Caucasians. J Hypertens. 1999;17:475–9.
63. Svetkey LP, Harris EL, Martin E, Vollmer WM, Meltesen GT, Ricchiuti V, et al. Modulation of the BP response to diet by genes in the renin-angiotensin system and the adrenergic nervous system. Am J Hypertens. 2011;24:209–17.
64. Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS, et al. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension: trials of hypertension prevention, phase II. Hypertension. 1998;32:393–401.
65. Hunt SC, Geleijnse JM, Wu LL, Witteman JC, Williams RR, Grobbee DE. Enhanced blood pressure response to mild sodium reduction in subjects with the 235T variant of the angiotensinogen gene. Am J Hypertens. 1999;12:460–6.
66. Norat T, Bowman R, Luben R, Welch A, Khaw KT, Wareham N, et al. Blood pressure and interactions between the angiotensin polymorphism AGT M235T and sodium intake: a cross-sectional population study. Am J Clin Nutr. 2008;88:392–7.
67. Iwai N, Kajimoto K, Tomoike H, Takashima N. Polymorphism of CYP11B2 determines salt sensitivity in Japanese. Hypertension. 2007;49:825–31.
68. Wrona A, Widecka K, Adler G, Czekalski S, Ciechanowicz A. Promoter variants of aldosterone synthase gene (CYP11B2) and salt-sensitivity of blood pressure. Pol Arch Med Wewn. 2004;111:191–7.
69. Pamies-Andreu E, Ramirez-Lorca R, García-Junco PS, Muniz-Grijalbo O, Vallejo-Maroto I, Morillo SG, et al. Renin-angiotensin-aldosterone system and G-protein beta-3 subunit gene polymorphisms in salt-sensitive essential hypertension. J Hum Hypertens. 2003;17:187–91.
70. Miyaki K, Hara A, Araki J, Zhang L, Song Y, Kimura T, et al. C3123A polymorphism of the angiotensin II type 2 receptor gene and salt sensitivity in healthy Japanese men. J Hum Hypertens. 2006;20:467–9.
71. Cicila GT, Garrett MR, Lee SJ, Liu J, Dene H, Rapp JP. High-resolution mapping of the blood pressure QTL on chromosome 7 using Dahl rat congenic strains. Genomics. 2001;72:51–60.
72. Lovati E, Ferrari P, Dick B, Jostarndt K, Frey BM, Frey FJ, et al. Molecular basis of human salt sensitivity: the role of the 11beta-hydroxysteroid dehydrogenase type 2. J Clin Endocrinol Metab. 1999;84:3745–9.
73. Agarwal AK, Giacchetti G, Lavery G, Nikkila H, Palermo M, Ricketts M, et al. CA-repeat polymorphism in intron 1 of HSD11B2: effects on gene expression and salt sensitivity. Hypertension. 2000;36:187–94.
74. Alikhani-Koupaei R, Fouladkou F, Fustier P, Cenni B, Sharma AM, Deter H-C, et al. Identification of polymorphisms in the human 11beta-hydroxysteroid dehydrogenase type 2 gene promoter: functional characterization and relevance for salt sensitivity. FASEB J. 2007;21:3618–28.
75. Zhao Q, Hixson JE, Rao DC, Gu D, Jaquish CE, Rice T, et al. Genetic variants in the apelin system and blood pressure responses to dietary sodium interventions: a family-based association study. J Hypertens. 2010;28:756–63.
76. Gu D, Kelly TN, Hixson JE, Chen J, Liu D, Chen JC, et al. Genetic variants in the renin-angiotensin-aldosterone system and salt sensitivity of blood pressure. J Hypertens. 2010;28:1210–20.
77. Rossier BC, Pradervand S, Schild L, Hummler E. Epithelial sodium channel and the control of sodium balance: interaction between genetic and environmental factors. Annu Rev Physiol. 2002;64:877–97.
78. Freitas SR. Molecular genetics of salt-sensitivity and hypertension: role of renal epithelial sodium channel genes. Am J Hypertens. 2017;31:172–4.
79. Adamzik M, Frey UH, Bitzer K, Jakob H, Baba HA, Schmieder RE, et al. A novel-1364A/C aquaporin 5 gene promoter polymorphism influences the responses to salt loading of the renin-angiotensin-aldosterone system and of blood pressure in young healthy men. Basic Res Cardiol. 2008;103:598–610.
80. Barlassina C, Dal Fiume C, Lanzani C, Manunta P, Guffanti G, Ruello A, et al. Common genetic variants and haplotypes in renal CLCNKA gene are associated to salt-sensitive hypertension. Hum Mol Genet. 2007;16:1630–8.
81. Citterio L, Simonini M, Zagato L, Salvi E, Carpini SD, Lanzani C, et al. Genes involved in vasoconstriction and vasodilation system affect salt-sensitive hypertension. PLoS One. 2011;6:e19620.
82. Manunta P, Lavery G, Lanzani C, Braund PS, Simonini M, Bodycote C, et al. Physiological interaction between alpha-

adducin and WNK1-NEDD4L pathways on sodium-related blood pressure regulation. Hypertension. 2008;52:366–72.
83. Osada Y, Miyauchi R, Goda T, Kasezawa N, Horiike H, Iida M, et al. Variations in the WNK1 gene modulates the effect of dietary intake of sodium and potassium on blood pressure determination. J Hum Genet. 2009;54:474–8.
84. Hoffmann IS, Tavares-Mordwinkin R, Castejon AM, Alfieri AB, Cubeddu LX. Endothelial nitric oxide synthase polymorphism, nitric oxide production, salt sensitivity and cardiovascular risk factors in Hispanics. J Hum Hypertens. 2005;19:233–40.
85. Carey RM, Schoeffel CD, Gildea JJ, Jones JE, McGrath HE, Gordon LN, et al. Salt sensitivity of blood pressure is associated with polymorphisms in the sodium-bicarbonate cotransporter. Hypertension. 2012;60:1359–66.
86. Rao AD, Sun B, Saxena A, Hopkins PN, Jeunemaitre X, Brown NJ, et al. Polymorphisms in the serum- and glucocorticoid-inducible kinase 1 gene are associated with blood pressure and renin response to dietary salt intake. J Hum Hypertens. 2013;27:176–80.
87. Zhao Q, Gu D, Hixson JE, Liu DP, Rao DC, Jaquish CE, et al. Common variants in epithelial sodium channel genes contribute to salt sensitivity of blood pressure: the GenSalt study. Circ Cardiovasc Genet. 2011;4:375–80.
88. Li C, Yang X, He J, Hixson JE, Gu D, Rao DC, et al. A gene-based analysis of variants in the serum/glucocorticoid regulated kinase (SGK) genes with blood pressure responses to sodium intake: The GenSalt Study. PLoS One. 2014;9:e98432.
89. Guo L, Liu F, Chen S, Yang X, Huang J, He J, et al. Common variants in the Na(+)-coupled bicarbonate transporter genes and salt sensitivity of blood pressure: the GenSalt study. J Hum Hypertens. 2016;30:543–8.
90. Liu Z, Qi H, Liu B, Liu K, Wu J, Cao H, et al. Genetic susceptibility to salt-sensitive hypertension in a Han Chinese population: a validation study of candidate genes. Hypertens Res. 2017;40:876–84.
91. Liu F, Zheng S, Mu J, Chu C, Wang L, Wang Y, et al. Common variation in with no-lysine kinase 1 (WNK1) and blood pressure responses to dietary sodium or potassium interventions—family-based association study. Circ J. 2013;77:169–74.
92. Toda N, Arakawa K. Salt-induced hemodynamic regulation mediated by nitric oxide. J Hypertens. 2011;29:415–24.
93. Dengel DR, Brown MD, Ferrell RE, Reynolds TH, Supiano MA. A preliminary study on T-786C endothelial nitric oxide synthase gene and renal hemodynamic and blood pressure responses to dietary sodium. Physiol Res. 2007;56:393–401.
94. Miyaki K, Tohyama S, Murata M, Kikuchi H, Takei I, Watanabe K, et al. Salt intake affects the relation between hypertension and the T-786C polymorphism in the endothelial nitric oxide synthase gene. Am J Hypertens. 2005;18:1556–62.
95. Castejon AM, Bracero J, Hoffmann IS, Alfieri AB, Cubeddu LX. NAD(P)H oxidase p22phox gene C242T polymorphism, nitric oxide production, salt sensitivity and cardiovascular risk factors in Hispanics. J Hum Hypertens. 2006;20:772–9.
96. Shindo T, Kurihara H, Maemura K, Kurihara Y, Ueda O, Suzuki H, et al. Renal damage and salt-dependent hypertension in aged transgenic mice overexpressing endothelin-1. J Mol Med. 2002;80:105–16.
97. Caprioli J, Mele C, Mossali C, Gallizioli L, Giacchetti G, Noris M, et al. Polymorphisms of EDNRB, ATG, and ACE genes in salt-sensitive hypertension. Can J Physiol Pharmacol Can. 2008;86:505–10.
98. Rhee M-Y, Yang SJ, Oh SW, Park Y, Kim C, Park H-K, et al. Novel genetic variations associated with salt sensitivity in the Korean population. Hypertens Res. 2011;34:606–11.
99. Manosroi W, Tan JW, Rariy CM, Sun B, Goodarzi MO, Saxena AR, et al. The association of estrogen receptor-beta gene variation with salt-sensitive blood pressure. J Clin Endocrinol Metab. 2017;102:4124–35.
100. Defagó MD, Gu D, Hixson JE, Shimmin LC, Rice TK, Gu CC, et al. Common genetic variants in the endothelial system predict blood pressure response to sodium intake: the GenSalt study. Am J Hypertens. 2013;26:643–56.
101. Han X, Hu Z, Chen J, Huang J, Huang C, Liu F, et al. Associations between genetic variants of nadph oxidase-related genes and blood pressure responses to dietary sodium intervention: the GenSalt study. Am J Hypertens. 2017;30:427–34.
102. Kedzierska K. Activity of the sodium-proton exchanger and polymorphism of G-protein beta-3 subunit in patients with essential hypertension. Ann Acad Med Stetin. 2004;50:75–86.
103. Schorr U, Blaschke K, Beige J, Distler A, Sharma AM. G-protein beta3 subunit 825T allele and response to dietary salt in normotensive men. J Hypertens. 2000;18:855–9.
104. Beeks E, Kessels AGH, Kroon AA, van der Klauw MM, de Leeuw PW. Genetic predisposition to salt-sensitivity: a systematic review. J Hypertens. 2004;22:1243–9.
105. Barlassina C, Schork NJ, Manunta P, Citterio L, Sciarrone M, Lanella G, et al. Synergistic effect of alpha-adducin and ACE genes causes blood pressure changes with body sodium and volume expansion. Kidney Int. 2000;57:1083–90.
106. Cusi D, Barlassina C, Azzani T, Casari G, Citterio L, Devoto M, et al. Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. Lancet. 1997;349:1353–7.
107. Glorioso N, Manunta P, Filigheddu F, Troffa C, Stella P, Barlassina C, et al. The role of alpha-adducin polymorphism in blood pressure and sodium handling regulation may not be excluded by a negative association study. Hypertension. 1999;34:649–54.
108. Grant FD, Romero JR, Jeunemaitre X, Hunt SC, Hopkins PN, Hollenberg NH, et al. Low-renin hypertension, altered sodium homeostasis, and an alpha-adducin polymorphism. Hypertension. 2002;39:191–6.
109. Manunta P, Cusi D, Barlassina C, Righetti M, Lanzani C, D'Amico M, et al. Alpha-adducin polymorphisms and renal sodium handling in essential hypertensive patients. Kidney Int. 1998;53:1471–8.
110. Manunta P, Maillard M, Tantardini C, Simonini M, Lanzani C, Citterio L, et al. Relationships among endogenous ouabain, alpha-adducin polymorphisms and renal sodium handling in primary hypertension. J Hypertens. 2008;26:914–20.
111. Sciarrone MT, Stella P, Barlassina C, Manunta P, Lanzani C, Bianchi G, et al. ACE and alpha-adducin polymorphism as markers of individual response to diuretic therapy. Hypertension. 2003;41:398–403.
112. Kelly TN, Rice TK, Gu D, Hixson JE, Chen J, Liu D, et al. Novel genetic variants in the alpha-adducin and guanine nucleotide binding protein beta-polypeptide 3 genes and salt sensitivity of blood pressure. Am J Hypertens. 2009;22:985–92.
113. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. Mayo Clin Proc. 2009;84:822–30.
114. Thomas P, Dasgupta I. The role of the kidney and the sympathetic nervous system in hypertension. Pediatr Nephrol. 2015;30:549–60.
115. Pojoga L, Kolatkar NS, Williams JS, Perlstein TS, Jeunemaitre X, Brown NJ, et al. Beta-2 adrenergic receptor diplotype defines a subset of salt-sensitive hypertension. Hypertension. 2006;48:892–900.
116. Sun B, Williams JS, Svetkey LP, Kolatkar NS, Conlin PR. Beta2-adrenergic receptor genotype affects the renin-angiotensin-aldosterone system response to the Dietary Approaches to Stop Hypertension (DASH) dietary pattern. Am J Clin Nutr. 2010;92:444–9.

117. Sanada H, Yatabe J, Midorikawa S, Hashimoto S, Watanabe T, Moore JH, et al. Single-nucleotide polymorphisms for diagnosis of salt-sensitive hypertension. Clin Chem. 2006;52:352–60.
118. Wainford RD, Carmichael CY, Pascale CL, Kuwabara JT. Galphai2-protein-mediated signal transduction: central nervous system molecular mechanism countering the development of sodium-dependent hypertension. Hypertension. 2015;65:178–86.
119. Zhang X, Frame AA, Williams JS, Wainford RD. GNAI2 polymorphic variance associates with salt sensitivity of blood pressure in the Genetic Epidemiology Network of Salt Sensitivity study. Physiol Genom. 2018;50:724–5.
120. Li L, Xu J, Chen L, Jiang Z. Apelin/APJ system: a novel promising therapy target for thrombotic diseases. Acta Biochim Biophys Sin. 2016;48:589–91.
121. Li WW, Niu WQ, Zhang Y, Wu S, Gao PJ, Zhu DL. Family-based analysis of apelin and AGTRL1 gene polymorphisms with hypertension in Han Chinese. J Hypertens. 2009;27:1194–201.
122. Ellis KL, Newton-Cheh C, Wang TJ, Frampton CM, Doughty RN, Whalley GA, et al. Association of genetic variation in the natriuretic peptide system with cardiovascular outcomes. J Mol Cell Cardiol. 2011;50:695–701.
123. Widecka K, Ciechanowicz A, Adler G, Szychot E, Wodecki M, Czekalski S. Analysis of polymorphisms Sma (Hpa II) and Sca I gene precursors of atrial natriuretic peptide (ANP) in patients with essential hypertension. Pol Arch Med Wewn. 1998;100:27–34.
124. Chen S, Huang J, Zhao Q, Chen J, Jaquish CE, He J, et al. Associations between genetic variants of the natriuretic peptide system and blood pressure response to dietary sodium intervention: the GenSalt study. Am J Hypertens. 2016;29:397–404.
125. Mei H, Gu D, Hixson JE, Rice TK, Chen J, Shimmin LC, et al. Genome-wide linkage and positional association study of blood pressure response to dietary sodium intervention: the GenSalt study. Am J Epidemiol. 2012;176(Suppl. 7):S81–90.
126. Gu D, Zhao Q, Kelly TN, Hixson JE, Rao DC, Cao J, et al. The role of the kallikrein-kinin system genes in the salt sensitivity of blood pressure: the GenSalt study. Am J Epidemiol. 2012;176 (Suppl. 7):S72–80.
127. Eap CB, Bochud M, Elston RC, Bovet P, Maillard MP, Nussberger J, et al. CYP3A5 and ABCB1 genes influence blood pressure and response to treatment, and their effect is modified by salt. Hypertension. 2007;49:1007–14.
128. Bochud M, Eap CB, Elston RC, Bovet P, Maillard M, Schild L, et al. Association of CYP3A5 genotypes with blood pressure and renal function in African families. J Hypertens. 2006; 24:923–9.
129. Ho H, Pinto A, Hall SD, Flockhart DA, Li L, Skaar TC, et al. Association between the CYP3A5 genotype and blood pressure. Hypertension. 2005;45:294–8.
130. Yagil C, Hubner N, Monti J, Schulz H, Sapojnikov M, Luft FC, et al. Identification of hypertension-related genes through an integrated genomic-transcriptomic approach. Circ Res. 2005;96:617–25.
131. Tian Z, Greene AS, Usa K, Matus IR, Bauwens J, Pietrusz JL, et al. Renal regional proteomes in young Dahl salt-sensitive rats. Hypertension. 2008;51:899–904.
132. Havlik RJ. Predictors of hypertension. Popul Stud Am J Hypertens. 1991;4:586S–589S.
133. Castrop H, Kurtz A. Differential nNOS gene expression in salt-sensitive and salt-resistant Dahl rats. J Hypertens. 2001;19:1223–31.
134. Fava C, Danese E, Montagnana M, Sjogren M, Almgren P, Engstrom G, et al. Serine/threonine kinase 39 is a candidate gene for primary hypertension especially in women: results from two cohort studies in Swedes. J Hypertens. 2011;29:484–91.
135. Garza AE, Rariy CM, Sun B, Williams J, Lasky-Su J, Baudrand R, et al. Variants in striatin gene are associated with salt-sensitive blood pressure in mice and humans. Hypertension. 2015;65:211–7.
136. He J, Kelly TN, Zhao Q, Li H, Huang J, Wang L, et al. Genome-wide association study identifies 8 novel loci associated with blood pressure responses to interventions in Han Chinese. Circ Cardiovasc Genet. 2013;6:598–607.
137. Muller DN, Dechend R, Mervaala EM, Park JK, Schmidt F, Fiebeler A, et al. NF-kappaB inhibition ameliorates angiotensin II-induced inflammatory damage in rats. Hypertension. 2000;35:193–201.
138. Rodríguez-Iturbe B, Ferrebuz A, Vanegas V, Quiroz Y, Mezzano S, Vaziri ND. Early and sustained inhibition of nuclear factor-kappaB prevents hypertension in spontaneously hypertensive rats. J Pharmacol Exp Ther. 2005;315:51–57.
139. Goldstein DB, Allen A, Keebler J, Margulies EH, Petrou S, Petrovski S, et al. Sequencing studies in human genetics: design and interpretation. Nat Rev Genet. 2013;14:460–70.
140. Kelly TN, Li C, Hixson JE, Gu D, Rao DC, Huang J, et al. Resequencing study identifies rare renin-angiotensin-aldosterone system variants associated with blood pressure salt-sensitivity: the GenSalt study. Am J Hypertens. 2017;30:495–501.
141. Gu X, Gu D, He J, Rao DC, Hixson JE, Chen J, et al. Resequencing epithelial sodium channel genes identifies rare variants associated with blood pressure salt-sensitivity: the GenSalt study. Am J Hypertens. 2018;31:205–11.
142. Rayner B, Ramesar R, Steyn K, Levitt N, Lombard C, Charlton K. G-protein-coupled receptor kinase 4 polymorphisms predict blood pressure response to dietary modification in Black patients with mild-to-moderate hypertension. J Hum Hypertens. 2012;26:334–9.
143. Chu C, Wang Y, Ren KY, et al. Genetic variants in adiponectin and blood pressure responses to dietary sodium or potassium interventions: a family-based association study. J Hum Hypertens. 2016;30:563–70.