Original Paper

Common Variants in Serum/Glucocorticoid Regulated Kinase 1 (SGK1) and Blood Pressure Responses to Dietary Sodium or Potassium Interventions: A family-Based Association Study

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Key Words

Serum/glucocorticoid regulated kinase 1 • Blood pressure • Sodium • Potassium • Single-nucleotide polymorphism

Abstract

Background/Aims: Serum/Glucocorticoid Regulated Kinase 1 (SGK1) plays a significant role in regulating renal Na⁺ reabsorption, K⁺ secretion, and blood pressure (BP). This study aimed to assess the association of common genetic variants in the SGK1 gene with BP responses to controlled dietary sodium or potassium interventions. **Methods:** A total of 334 subjects from 124 families were recruited from the rural areas of northern China. After a three-day baseline observation, they were sequentially maintained a seven-day low-sodium diet (3g/day of NaCl or 51.3mmol/day of sodium), a seven-day high-sodium diet (18g/day of NaCl or 307.8 mmol/day of sodium) and a seven-day high-sodium plus potassium supplementation intervention (4.5g/day of KCl or 60mmol/day of potassium). Six single-nucleotide polymorphisms (SNPs) in the SGK1 gene were selected. **Results:** After adjustment for multiple testing, SNP rs9376026 was significantly associated with diastolic BP (DBP) and mean arterial pressure (MAP) responses to low-sodium intervention (P = 0.018 and 0.022, respectively). However, the associations between selected SNPs in the SGK1 gene and BP responses to high-sodium or high-sodium plus potassium-supplementation intervention did not reach statistical significance. In addition, SNP rs9389154 and two other SNPs (rs1763509 and rs9376026) were associated respectively with systolic BP (SBP) and DBP at baseline (P = 0.040, 0.032, and 0.031, respectively). SNP

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rs3813344 was significantly associated with SBP, DBP, and MAP ($P = 0.049$, 0.015 and 0.018 , respectively). **Conclusion:** Our study indicates that the genetic polymorphism in the SGK1 gene is significantly associated with BP responses to dietary sodium intervention.

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Introduction

High blood pressure (BP) is the leading preventable risk factor for cardiovascular diseases, accounting for approximately 47% of ischemic heart diseases and 54% of strokes worldwide [1]. Interactions among numerous genetic and environmental factors play an important role in BP regulation. Observational epidemiologic studies have reported that BP is positively correlated with dietary sodium intake and inversely associated with dietary potassium intake [2-4]. However, BP responses to dietary sodium intake or potassium supplementation vary considerably among individuals [5, 6]. Sizeable evidence suggests that the genetic profile of an individual may contribute to this phenomenon [6, 7]. Thus, discovering novel genetic variants related to BP responses to dietary sodium or potassium intake can help us better understand the biological mechanisms of BP regulation.

Serum/glucocorticoid regulated kinase 1 (SGK1), a member of the AGC family of serine/threonine protein kinases, was first identified as a gene transcriptionally controlled by serum and glucocorticoids in rat Con8 mammary epithelial tumor cells [8]. The gene (148, 813 bp) contains 17 exons and is located on chromosome 6 at q23 (Gene ID: 6446). The SGK1 protein is expressed in virtually all tissues, predominantly in those involved in water and electrolyte reabsorption, such as renal and colonic mucosa [9, 10]. Accordingly, SGK1 contributes to a variety of pathological processes, such as renal tissue fibrosis, colonic tumor growth, vascular inflammation, and atherogenesis [11-13]. Moreover, it participates in the regulation of renal sodium reabsorption, potassium elimination and thus potentially blood pressure by aldosterone, which affects various transport systems, including Na^+ / H^+ exchanger 3 in proximal tubule, epithelial Na^+ channel, Na^+ - Cl^- cotransporter, and renal outer-medullary K^+ channel 1 in distal convoluted tubule and collecting duct, and basolateral Na^+ - K^+ -ATPase in all nephron segments [14-18]. Animal studies showed that, compared with wild-type mice, SGK1-knockout ($\text{SGK1}^{-/-}$) mice have higher urinary flow rate, increased Na^+ excretion, hyperkalemia, lower BP, and significantly increased plasma aldosterone levels under a low- Na^+ diet [19]. Epidemiological studies also found an association between a certain SGK1 gene variant (combined polymorphisms in intron 6 [I6CC] and in exon 8 [E8CC/CT]) and moderately enhanced BP in white Germans [20]. These data suggested that SGK1 genetic variants contribute to BP variations and/or to susceptibility to essential hypertension. However, few studies considered the gene and environment interactions, especially dietary salt and potassium, on BP. Owing to the interference between gene and environment interactions, the genetic contribution to BP variability is difficult to detect fully in those studies. In view of this limitation, our study aimed to assess the association of common genetic variants in the SGK1 gene with BP responses to controlled dietary sodium or potassium interventions of 334 normotensive or pre-hypertensive subjects from rural northern China.

Participants and Methods

Subjects

This investigation involved a family-based dietary feeding study conducted in a Han Chinese population from the rural areas of northern China. The potential probands and their families were identified by a community-based BP screening conducted among adults aged 18–60 years in the study villages. The

probands who had a mean systolic BP (SBP) between 130-160 mmHg and/or a diastolic BP (DBP) between 85-100 mmHg and no use of antihypertensive medications and their siblings, spouses, and offspring were recruited for the dietary intervention study. The exclusion criteria were secondary hypertension, stage-2 hypertension, a history of clinical cardiovascular disease or diabetes, used antihypertensive medications, or were pregnant, heavy alcohol drinkers, or currently on a low-sodium diet, or unable to sign the informed consent form.

The institutional ethics committee of Xi'an Jiaotong University Medical School approved the study protocol, and written informed consent for the baseline observation and for the intervention program was obtained from each participant. All of the procedures were performed in accordance with institutional guidelines.

Dietary intervention

The chronic salt loading and potassium-supplementation intervention program was carried out as previously described [21]. Briefly, after a three-day baseline examination including a questionnaire survey and measurements of BP, height, weight and blood biochemical parameters, the study participants sequentially received a seven-day low-sodium diet (3g/day of NaCl or 51.3mmol/day of sodium), a seven-day high-sodium diet (18g/day of NaCl or 307.8 mmol/day of sodium) and a seven-day high-sodium plus potassium supplementation intervention (4.5g/day of KCl or 60mmol/day of potassium). All foods were cooked without salt, and prepackaged salt was added to the meal of each participant when it was served by the study staff. During the entire study period, other dietary nutrient intakes remained unchanged. To ensure the compliance of participants to the intervention program, they were required to have their three meals (breakfast, lunch, and dinner) in the study kitchen. The participants were also given detailed instructions to avoid consuming food not provided by the study.

Determination of 24-hour urinary sodium and potassium excretions

One 24-hour urinary specimen was collected at baseline and at the end of each intervention period to ensure the compliance of participants to the dietary intervention. The concentrations of sodium and potassium in the urine sample were measured by a flame photometer. The 24-hour urinary sodium and potassium excretions of each subject were calculated as the measured concentration of sodium or potassium multiplied by total volume of individual's 24-hour urine.

BP measurements

Three BP measurements were obtained using a random-zero sphygmomanometer (Hawksley & Sons Ltd, Lancing, UK) at each morning of 3-day baseline examination as well as on days 5, 6, and 7 of each dietary period, and BP was measured by the trained and certified observers according to a common protocol [22]. Study participants were required to avoid cigarette smoking, alcohol, coffee/tea, and Strenuous exercise for at least 30 minutes before their BP measurement. BP measurement was taken in a sitting position after a 5-min rest. The first and fifth phases of the Korotkoff sounds were taken as SBP and DBP, respectively. Three BP measurements each day were performed with an interval of 1-min and the mean values of nine BP measurements during the baseline survey or each intervention period were recorded as the BP levels at baseline and each intervention period. In addition, MAP was calculated according to the following formula: $MAP = DBP + 1/3(SBP - DBP)$. In the present study, BP responses were considered as continuous variables and defined as follows: BP response to low sodium = BP on low-sodium diet minus BP at baseline; BP response to high sodium = BP on high-salt diet minus BP on low-salt diet; and BP response to potassium supplementation = BP on high-salt diet with potassium supplementation minus BP on high-salt diet.

SGK1 SNP Selection and Genotyping

Six tagSNPs in the SGK1 gene with a minor allele frequency (MAF) of more than 5% in the Chinese Han of Beijing HapMap databank (www.hapmap.org/) were selected as the study sites. Genomic DNA was extracted from whole blood specimen collected from each participant using the GOLDMAG Whole Blood Genomic DNA Purification Kit (Golden Magnetic Nano-Biotechnology Co., Ltd. Xi'an, China). PCR primers and single base extension primers required for SNP genotyping were designed by MassARRAY Assay

Design software (version 3.0) and synthesized by Shanghai Biological Technology Co., Ltd. (<http://www.sangon.com/>). The genotyping experiments were done by Xi'an BaiMei genetic testing center (<http://www.lifegen.com/>) using a MassARRAY system (Sequenom, San Diego, CA, USA) based on the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry method, according to the manufacturer's instructions. Genotype calling was performed in real time with MassARRAY RT software (version 3.1) and analyzed using the MassARRAY Typer software version 4.0 (Sequenom).

Statistical analysis

Continuous data are presented as mean $\pm$ standard error. Categorical data are expressed as frequency with percentage. Differences in repeated measures were analyzed by Paired samples t-test. The Mendelian consistency of the single-nucleotide polymorphism (SNP) genotype data was assessed using PLINK [23]. We used Haploview software (version 4.0, <http://www.broad.mit.edu/mpg/haploview>) to test Hardy-Weinberg equilibrium on parental SNP data and estimate the extent of pairwise linkage disequilibrium (LD) between SNPs. LD blocks were defined using the solid spine LD method implemented in Haploview software [24]. The association of single markers with adjusted phenotypes was investigated using a family-based association test (FBAT; version 2.0.2, <http://www.biostat.harvard.edu/fbat/default.html>) and three genetic models (additive, dominant, and recessive) were adopted in each SNP analysis [25]. To assess the effect of genetic variants on the trait value, a univariate FBAT test was performed for each allele and haplotype. This test provides a Z-statistic with its corresponding P-value. In the present study, a positive Z-statistic for an allele or a haplotype indicated a decreased response to the low-sodium intervention and high-sodium plus potassium-supplementation intervention, an increased response to high-sodium intervention, and an increase in basal BP. The false discovery rate (FDR) method was used to correct for multiple testing [26]. A q-value of 0.05 was the threshold for statistical significance in our study.

Results

Baseline characteristics and BP responses to dietary intervention

Table 1 shows the baseline characteristics and BP responses to the low-sodium, high-sodium, and high-sodium plus potassium-supplementation interventions of study participants. The mean levels of baseline systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) in the proband group were higher than those in the sibling, spouse, and offspring groups. The baseline SBP level of the parent group, however, was the highest among those of all the groups. Overall, BP levels were reduced and increased respectively in response to the low-sodium and high-sodium interventions, and BP levels were again reduced in response to the high-sodium plus potassium-supplementation intervention.

Influence of dietary intervention on 24-hour urinary sodium and potassium excretions

The influence of dietary intervention on 24-hour urinary sodium and potassium excretions are shown in Table 2. To ensure the compliance of participants to the intervention program, the sodium and potassium values in 24-hour urine were calculated at baseline and at the end of each diet period. The 24-hour urinary sodium and potassium excretions at baseline indicated that the diet of the participants featured high sodium and low potassium. The 24-hour urinary sodium excretion reduced from baseline to low-sodium diet but markedly increased from low-sodium to high-sodium diet. The 24-hour urinary sodium and potassium excretions were slightly increased by high-sodium and potassium supplementation. This result showed excellent compliance with the dietary intervention.

Information on genotyped SNPs in SGK1

Table 3 shows the information on the genotyped SNPs in SGK1, including genomic location, allele frequency, and Hardy-Weinberg equilibrium test results for the six SNPs in SGK1. No SNP deviated from the Hardy-Weinberg equilibrium ($P > 0.05$).

Table 1. Characteristics of participants

	Probands	Siblings	Spouses	Offspring	Parents	Non-parents [†]
NO. of subjects	99	167	19	49	181	334
Age, year	41.8±8.4	39.8±7.4	47.4±6.1	23.3±6.9	66.1±8.3	38.4±9.9
Male, %	69.7	49.1	26.3	49.0	48.4	53.5
BMI, kg/m ²	23.0±2.8	22.2±2.9	23.1±4.7	20.1±2.7	—	22.2±3.1
Baseline BP, mmHg						
SBP	120.9±12.5	107.6±11.1	108.6±12.2	102.7±10.7	123.2±21.3	110.9±13.3
DBP	78.9±8.3	70.1±8.1	70.6±6.9	63.4±8.9	70.5±10.5	71.8±9.7
MAP	93.0±9.0	82.6±8.7	83.3±7.9	76.5±9.2	88.0±13.1	84.8±10.4
BP response to low-sodium intervention, mmHg						
SBP	111.7±10.0*	103.4±9.1*	102.5±7.7*	100.3±9.4*	—	105.4±10.2*
DBP	72.8±9.3*	66.4±7.7*	67.1±5.8 [#]	60.7±8.3*	—	67.5±9.1*
MAP	85.7±9.0*	78.7±7.6*	78.9±5.4 [#]	73.9±8.3 [#]	—	80.1±9.0*
SBP change	-8.65±9.52	-3.90±5.41	-6.15±7.88	-2.38±4.79	—	-5.20±7.31
DBP change	-6.00±6.71	-3.64±4.83	-3.48±6.36	-2.70±5.21	—	-4.19±5.69
MAP change	-6.88±7.07	-3.73±4.55	-4.37±6.52	-2.59±4.56	—	-4.53±5.73
BP response to high-sodium intervention, mmHg						
SBP	118.9±11.2	108.5±11.1 [#]	108.4±10.9	102.0±10.0	—	110.6±12.4
DBP	76.2±8.1*	68.7±9.3*	68.6±7.5	60.9±8.3*	—	69.8±10.0*
MAP	90.4±8.5*	82.0±9.5	81.9±8.0	74.6±8.4*	—	83.4±10.4*
SBP change	7.16±7.40	5.09±6.50	5.93±7.90	1.72±4.07	—	5.25±6.77
DBP change	3.49±7.33	2.29±5.73	1.51±4.69	0.22±4.52	—	2.30±6.12
MAP change	4.71±6.86	3.22±5.60	2.98±5.61	0.72±3.79	—	3.28±5.90
BP response to high-sodium plus potassium intervention, mmHg						
SBP	112.2±8.6*	103.1±8.9*	102.8±9.4*	101.0±9.6 [#]	—	105.5±10.0*
DBP	73.0±7.7*	66.1±7.9*	65.9±7.1	59.9±8.0*	—	67.2±8.9*
MAP	86.1±7.4*	78.4±7.8*	78.2±7.2*	73.6±8.1*	—	79.9±8.8*
SBP change	-6.54±5.65	-5.48±5.86	-5.59±7.10	-1.02±4.15	—	-5.13±5.90
DBP change	-3.21±4.76	-2.63±4.88	-2.69±4.42	-1.02±4.25	—	-2.56±4.76
MAP change	-4.32±4.40	-3.58±4.77	-3.66±5.05	-1.02±3.35	—	-3.42±4.60

Variables are indicated as mean ± standard deviation; BP, blood pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. [†]All subjects except for parents, * $P < 0.01$ and [#] $P < 0.05$ vs. the value of baseline period.

Table 2. Influence of dietary intervention to urinary sodium and potassium excretions

	Probands	Siblings	Spouses	Offspring	Total
Baseline, mmol					
24 h Urinary sodium	225±11.6	213.8±16.4	218.3±20.8	205.4±23.4	215.7±19.2
24 h Urinary potassium	36.8±10.8	38.1±9.1	39.4±12.3	35.8±15.7	37.6±12.1
Low-sodium intervention, mmol					
24 h Urinary sodium	54.9±11.3*	53.6±9.8*	52.8±13.5*	58.2±15.1*	54.9±11.2*
24 h Urinary potassium	35.4±8.9 [#]	39.8±7.6 [#]	34.2±6.7*	40.5±9.8*	37.0±9.8
High-sodium intervention, mmol					
24 h Urinary sodium	317.0±21.8*	304.4±28.6*	318.6±20.5*	298.4±25.1*	310.0±27.0*
24 h Urinary potassium	43.4±13.9*	39.6±9.1	40.2±8.3	41.1±14.5*	41.1±11.9*
High-sodium plus potassium-supplementation intervention, mmol					
24 h Urinary sodium	319.8±24.2*	331.2±25.9*	324.7±28.4*	327.3±21.8*	325.8±27.4*
24 h Urinary potassium	86.8±9.6*	79.3±11.5*	94.6±12.9*	87.5±10.7*	87.1±12.9*

Variables are indicated as mean ± standard deviation. * $P < 0.01$ and [#] $P < 0.05$ vs. the value of baseline period.

Associations between SGK1 SNPs and BP responses to dietary intervention and baseline BP

The associations between SNPs and BP responses to low-sodium, high-sodium, and high-sodium plus potassium-supplementation interventions are shown in Table 4. SNP

Table 3. Information on Genotyped SNPs of SGK1

SNP	Region in Gene	Position	Alleles [†]	MAF [‡]	HW P-values [‡]
rs1763509	Intron2	134554338	A/G	0.262431	0.0864
rs4896033	Intron2	134577726	G/A	0.129121	0.4953
rs9376026	Intron1	134602454	C/T	0.171271	0.376
rs9389154	Intron1	134614761	A/G	0.450549	0.3603
rs4409196	Intron1	134630634	C/G	0.406077	0.7223
rs3813344	Exon1	134638966	G/C	0.070225	0.8884

SNP, single nucleotide polymorphism; MAF, Minor allele frequency; HW, Hardy-Weinberg equilibrium test. [†]Major allele/ minor allele. [‡]parental generation.

Table 4. SNPs associated with BP Response to Dietary Intervention

SNP	Allele†	SBP response		DBP response		MAP response	
		Z	P-value	Z	P-value	Z	P-value
Low-sodium intervention							
rs1763509	G	0.178	0.859	1.007	0.314	0.773	0.44
rs4896033	A	0.533	0.594	-0.948	0.343	-0.416	0.677
rs9376026	T	0.258	0.796	2.359	0.018^a	2.286	0.022^a
rs9389154	G	-0.262	0.793	0.023	0.981	-0.098	0.922
rs4409196	G	-0.369	0.712	-0.376	0.708	-0.405	0.686
rs3813344	C	-0.657	0.511	-0.696	0.487	-0.751	0.453
High-sodium intervention							
rs1763509	G	0.386	0.700	0.430	0.667	0.443	0.658
rs4896033	A	0.482	0.630	-0.591	0.555	-0.243	0.808
rs9376026	T	-0.030	0.976	0.412	0.681	0.291	0.771
rs9389154	G	0.383	0.701	0.119	0.905	0.223	0.823
rs4409196	G	0.732	0.464	0.258	0.796	0.447	0.655
rs3813344	C	0.207	0.836	0.145	0.884	0.18	0.858
High-sodium plus potassium supplementation intervention							
rs1763509	G	-0.491	0.623	-0.005	0.996	-0.191	0.849
rs4896033	A	0.472	0.637	0.864	0.388	0.826	0.409
rs9376026	T	0.178	0.859	-1.293	0.196	-0.896	0.37
rs9389154	G	-1.762	0.078^c	0.694	0.488	-0.044	0.964
rs4409196	G	-0.963	0.336	1.110	0.267	0.435	0.664
rs3813344	C	-0.901	0.368	-0.476	0.634	-0.681	0.496

For associations that were not significant under any model (additive model, dominant model and recessive model), Z and P values for an additive model are listed. All genetic models are based on the minor allele of each SNP. SNP, single nucleotide polymorphism; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Z indicates test statistic for Family-Based Association Test (FBAT); P-values are corrected for multiple testing (FDR<0.05). [†] minor allele, ^a additive model, ^c recessive model.

rs9376026 was significantly associated with DBP and MAP responses to low-sodium intervention (P = 0.018 and P = 0.022, respectively) after adjustment for multiple testing. Regretfully, associations between the six SNPs and BP responses to high-sodium and high-sodium plus potassium-supplementation interventions did not reach nominal statistical significance. In addition, Haploview software was used to construct haplotype blocks of the six SNPs, but none were constructed because of the weak LD between these SNPs in the study participants (Figure 1). Therefore, the associations of the SGK1 haplotypes with BP responses to dietary intervention could not be analyzed further.

Fig. 1. Linkage disequilibrium structure of the SGK1 gene. The black boxes in gene represent exons. Solid lines show introns and dashed lines show gene flanking regions. pairwise linkage disequilibrium (LD) coefficients $D' \times 100$ are shown in each cell (D' values of 1.0 are not shown) and The r^2 color scheme of Haploview was applied ($r^2 = 0$ shown in white, $0 < r^2 < 1$ shown in shades of gray, and $r^2 = 1$ shown in black).

Table 5. SNPs significantly associated with basal BP

SNP	Alleles [†]	SBP		DBP		MAP	
		Z	P-value	Z	P-value	Z	P-value
rs1763509	G	-0.553	0.581	2.142	0.032^c	-0.346	0.730
rs4896033	A	0.593	0.553	0.266	0.790	0.424	0.672
rs9376026	T	1.079	0.281	2.157	0.031^c	1.526	0.127
rs9389154	G	2.052	0.04^b	0.331	0.741	-0.127	0.899
rs4409196	G	-0.673	0.501	0.096	0.923	-0.23	0.818
rs3813344	C	-1.960	0.049^a	-2.43	0.015^a	-2.362	0.018^a

For associations that were not significant under any model (additive model, dominant model and recessive model), Z and P values for an additive model are listed. All genetic models are based on the minor allele of each. Abbreviations as in Table 4, † minor allele, a additive model, b dominant model, c recessive model.

Table 5 shows the associations of the SNPs with the baseline SBP, DBP, and MAP of the study participants. After adjustment for multiple testing, SGK1 SNP rs9389154 and two other SNPs (rs1763509 and rs9376026) were respectively associated with baseline SBP and DBP ($P = 0.040, 0.032$ and 0.031 , respectively). SGK1 SNP rs3813344 was significantly associated with baseline SBP, DBP, and MAP ($P = 0.049, 0.015$ and 0.018 , respectively).

Discussion

In this study, we identified several genetic variants in the SGK1 gene that may play an important role in basal BP and BP responses to dietary sodium intake. SNP rs9376026 of the SGK1 gene showed a significant influence on DBP and MAP responses to low-sodium intervention. SNP rs9389154 and two other SNPs (rs1763509 and rs9376026) were also respectively associated with SBP and DBP at baseline. SNP rs3813344 in the SGK1 gene was significantly associated with baseline SBP, DBP, and MAP. These findings may help us gain a better understanding of the genetic mechanisms underlying BP regulation.

In vivo, SGK1 stimulates renal sodium reabsorption as well as salt appetite thus affecting BP [27, 28]. The effects of this kinase are observed in SGK1^{-/-} mouse. Under a standard Na⁺ diet, the renal water and Na⁺/K⁺ excretions in doxycycline-treated kidney-specific SGK1^{-/-} mice have a tendency to be higher than those in wild-type control mice, whereas under a low-Na⁺ diet, the SGK1^{-/-} mice have lower BP, increased Na⁺ excretion, and hyperkalemia [16]. Ackermann and colleagues tested the in vivo efficacy of a novel SGK1 inhibitor (EMD638683) in mice and found that it could significantly decrease BP in fructose/saline-treated mice but not in SGK1^{-/-} mice or in control animals [29]. In addition, the role of SGK1 in BP regulation was demonstrated in studies on SGK1 gene polymorphism. A previous study reported that a genotype combination [the intron 6 (I6CC) and the exon 8 (E8CC/CT)] in the SGK1 gene was associated with moderately enhanced BP in 232 non-obese, normotensive white Germans [30]. Wownern et al. [31] conducted a cross-sectional study of 4608 unrelated subjects (2996 hypertensive patients and 1612 normotensive subjects) to verify this finding, and reached a consistent conclusion. In the current study, we first explored the association between SGK1 gene polymorphisms and baseline BP of a Chinese Han population, and then found that four SNPs (rs9389154, rs1763509, rs9376026 and rs3813344) in the SGK1 gene were significantly associated with BP, which provided further evidence of the participation of the SGK1 gene in BP regulation.

SGK1 gene polymorphisms are closely related to BP, and may play an important role in the salt sensitivity of BP. Rao et al. [32] found that two SGK1 genetic variants (rs2758151 and rs9402571) were associated with SBP response to high-sodium intervention in a Caucasian population. An association between SGK1 marker rs2758151 and BP response to salt dietary intervention in a homogenous Han Chinese population was also demonstrated by Li and colleagues [33]. However, SNP rs2758151, as reported by Li et al. [33], was associated with DBP response rather than with SBP response, as reported by Rao et al. [32]. The differences in study populations, and racial and intervention methods adopted in the two studies may have caused the discrepant results. In the present study, rs9376026 in the SGK1 gene was found to be significantly associated with DBP and MAP responses to low-sodium intervention. This gene locus was also examined in Li's study [31], but no statistically significant association was found between this locus and BP response to low- or high-sodium intervention. The discrepancy could be due to the different study populations or small sample size in our study. Further studies are needed to validate the role of this gene locus in the salt sensitivity of BP. Although the aforementioned findings vary, all of them suggest that the common variants of the SGK1 gene may play an important role in determining BP response to dietary sodium intake.

Epidemiology studies suggested that dietary potassium intake is inversely related to BP, and BP responses to the potassium intake of individuals within populations are heterogeneous [5, 6]. Previous evidence indicated that SGK1 is also a regulator of renal potassium excretion and, therefore, of potassium homeostasis in the body. Huang et al. [34] reported that plasma K⁺ concentration in wild-type mice was not significantly modified by either a high or low K⁺ diet. However, in Sgk1^{-/-} mice, a high K⁺ diet significantly enhanced plasma K⁺ concentration, despite plasma aldosterone concentration reaching values about sixfold higher than in wild-type mice. Significant association of SNPs in APLN and ACE2 genes with BP response to dietary potassium supplementation were also found in the Gensalt study [7]. Gu and colleagues showed that a moderate heritability of BP response to potassium supplementation existed in a Chinese population [21]. These studies suggested that genetic factors may contribute to the variation in BP responses to potassium intake. Given the important role of SGK1 in BP regulation and K⁺ metabolism, the SGK1 gene polymorphisms may also have a significant influence on BP response to dietary potassium supplementation. In the first investigation on the association between SGK1 genetic variants and BP response to potassium intake in a

Chinese Han population, we observed an association between rs9389154 and SBP response, albeit not significant. Large multi-center studies are necessary to confirm the role of SGK1 gene polymorphisms on BP responses to potassium intervention.

Our study possesses several strengths. First, our study was carried out in a Chinese Han population. Thus, the bias caused by population stratification is unlikely. Study participants who live in a homogenous environment have similar lifestyles and eating habits. BP responses to dietary intervention were also measured under a controlled dietary sodium intake or potassium supplementation. Thus phenotypic variance caused by environmental factors is reduced. Finally, compliance with a dietary intervention program assessed by 24-hour urinary sodium and potassium excretions was excellent. Despite its strengths, this study also has limitations. As the findings were derived from a Chinese Han population, they may not be generalizable to other populations because of the underlying differences in LD structure. Therefore, our findings need to be validated or replicated in different populations. Furthermore, aldosterone participates in the regulation of SGK1 expression and activity. However, the plasma or urinary concentration of aldosterone was not measured, and thus the relationship of SGK1 genotype with aldosterone level could not be established. As the molecular consequences of the SNPs are still unclear, further functional studies are also needed to clarify the influence of each SNP on SGK1.

Conclusion

Our study identified that the genetic polymorphism in SGK1 gene is significantly associated with BP responses to dietary sodium intervention. The results of our study suggested that the SGK1 gene may be mechanistically involved in salt-sensitivity phenotypes.

Disclosure Statement

The authors declared no conflict of interest. We emphasize that we referred to the subject dietary intervention methods adopted in the Gensalt study.

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