Common Genetic Variants in the Endothelial System Predict Blood Pressure Response to Sodium Intake: The GenSalt Study

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BACKGROUND
We examined the association between 14 endothelial system genes and salt-sensitivity of blood pressure (BP).

METHODS
After a 3-day baseline examination, during which time the usual diet was consumed, 1,906 Chinese participants received a 7-day low-sodium diet (51.3 mmol of sodium/day) followed by a 7-day high-sodium diet (307.8 mmol of sodium/day). BP measurements were obtained at baseline and at the end of each intervention using a random-zero sphygmomanometer.

RESULTS
The *DDAH1* rs11161637 variant was associated with reduced BP salt sensitivity, conferring attenuated systolic BP (SBP) and mean arterial pressure (MAP) decreases from baseline to the low-sodium intervention (both $P = 2\times10^{-4}$). Examination of genotype–sex interactions revealed that this relation was driven by the strong associations observed in men (P for interactions = 1.10×10^{-4} and 0.008, respectively). When switching from the low- to high-sodium intervention, increases in diastolic BP (DBP) and MAP were attenuated by the *COL18A1* rs2838944 minor A allele ($P = 1.41\times10^{-4}$ and 1.55×10^{-4}, respectively). Conversely, the *VWF* rs2239153 C variant was associated with increased salt sensitivity, conferring larger DBP and MAP reductions during low-sodium intervention ($P = 1.22\times10^{-4}$ and 4.44×10^{-5}, respectively). Ten variants from 3 independent *SELE* loci displayed significant genotype–sex interactions on DBP and MAP responses to low-sodium (P for interaction = 1.56×10^{-3} to 1.00×10^{-4}). Among men, minor alleles of 4 correlated markers attenuated BP responses to low-sodium intake, whereas minor alleles of another 4 correlated markers increased BP responses. No associations were observed in women for these variants. Further, qualitative interactions were shown for 2 correlated *SELE* markers.

CONCLUSIONS
These data support a role for the endothelial system genes in salt sensitivity.

Keywords: blood pressure; endothelial system; genes; hypertension; salt sensitivity.

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Hypertension is a major global health challenge because of its high prevalence and related risk of cardiovascular disease (CVD).[1,2] As a complex trait, hypertension susceptibility is influenced by the interaction of genetic and environmental factors.[3] Among environmental determinants, dietary sodium intake is one of the most important risk factors for hypertension.[4,5] Clinical trials, observational epidemiologic studies, and animal experiments have long demonstrated the

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causal relationship between high dietary sodium intake and elevated blood pressure (BP).[6–9] However, there is substantial evidence suggesting that BP responses to dietary sodium intake vary considerably among individuals and are normally distributed in populations.[10] This phenomenon can be described as BP salt sensitivity.

The role of the endothelial system in BP regulation by nitric oxide (NO)–mediated vasodilation has been well described.[11,12] Recently, studies have also shown that endothelial cells modify their function in response to changes in extracellular concentrations of sodium, with increased sodium related to decreased endothelial NO release and increased endothelial cell stiffness.[11,12] Although these data implicate the endothelial system in the pathogenesis of salt-sensitive hypertension, few studies have examined the relationship between endothelial system genes and BP response to dietary sodium intake.[13–16]

This study aimed to comprehensively examine the association between common genetic variants from 14 endothelial system candidate genes (Table 1) and systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) responses to a dietary sodium intervention among 1,906 participants of the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) feeding study.

METHODS

Study population

The GenSalt study was conducted in a Han Chinese population from rural north China where habitual salt intake is high. A community-based BP screening was conducted among adults aged 18–60 years in the study villages to identify potential probands and their families. Those with mean SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg and no use of antihypertension medications and their spouses, siblings, and offspring were recruited as volunteers for the dietary intervention study. Detailed eligibility criteria for the probands and siblings/spouses/offspring have been presented elsewhere.[6] Briefly, individuals with stage 2 hypertension, current or recent use of antihypertension medications, secondary hypertension, history of clinical CVD, diabetes, chronic kidney failure, and liver disease or peptic ulcer disease requiring treatment during the previous 2 years, along with pregnant women, heavy alcohol drinkers, and those currently adhering to a low-sodium diet or unable to sign the informed consent form, were excluded from the study. Among the 1,906 eligible participants from 633 families, 1,871 (98.2%) and 1,860 (97.6%) completed the low-sodium and high-sodium dietary interventions, respectively, and were included in the current analysis.

Dietary intervention

After a 3-day baseline examination, during which time the usual diet was consumed, study participants received a 7-day low-sodium diet (3 g of salt or 51.3 mmol of sodium/day) followed by a 7-day high-sodium diet (18 g of salt or 307.8 mmol of sodium/day). During both intervention phases, potassium intake remained unchanged. Total energy intake was varied according to each participant's baseline energy intake. All study foods were cooked without salt, and pre-packaged salt was added to the individual study participant's meal when it was served by the study staff. To ensure study participants' compliance with the intervention program, they were required to have their breakfast, lunch, and dinner at the study kitchen under supervision of the study staff during the entire study period. Three timed urinary specimens were collected at baseline and at the end of each intervention phase (days 5, 6, and 7) to monitor each participants' compliance with the dietary sodium intervention. The mean of 24-hour urinary excretions of sodium and potassium were 242.4 (SD = 66.7) mmol and 36.9 (SD = 9.6) mmol at baseline, 47.5 (SD = 16.0) mmol and 31.4 (SD = 7.7) mmol during the low-sodium intervention, and 244.3 (SD = 37.7) mmol and 35.7 (SD = 7.5) mmol during the high-sodium intervention, respectively.

Phenotype measurements

A standard questionnaire was administered by trained staff at the baseline examination to collect information on family structure, demographic characteristics, personal and family medical history, and lifestyle risk factors. Three morning BP measurements were obtained according to a standard protocol during each of the 3 days of baseline observation and on days 5, 6, and 7 of each intervention period. All BP readings were measured by trained and certified observers using a random zero sphygmomanometer.[17] BP was measured with the participant in the sitting position after 5 minutes of rest. In addition, participants were advised to avoid alcohol, cigarette smoking, coffee/tea, and exercise for at least 30 minutes before their BP measurements. All BP observers were blinded to the participant's dietary intervention. Body weight and height were measured twice in light indoor clothing without shoes during the baseline examination. Body mass index was calculated as kilograms per meters squared.

Salt-sensitivity phenotypes were defined continuously as the absolute changes in SBP, DBP, and MAP when switching from baseline to low-sodium intervention and from low-sodium to high-sodium intervention. Mean BP responses to low-sodium intake were calculated as the mean of 9 measurements on days 5, 6, and 7 during the low-sodium intervention minus the mean of 9 measurements at baseline, and responses to high-sodium intake were calculated as the mean of 9 measurements on days 5, 6, and 7 during the high-sodium intervention minus the mean of 9 measurements on days 5, 6, and 7 during the low-sodium intervention.

Candidate gene selection and single nucleotide polymorphism genotyping

We conducted a Medline literature search using Medical Subject Heading term "endothelium" or keywords "endothelial" or "endothelium" and Medical Subject Heading terms "genes" or "polymorphism, single nucleotide." Fourteen candidate genes in the endothelial system were identified by the literature search strategy, including *VCAM1, EDN2, DDAH1, SELE, EDNRA, MEF2C, EDN1, SERPINE 1, NOS3, VWF, EDNRB, CYBA, TGFB1,* and *COL18A1* (see Table 1). References of articles used to identify genes can be found

Table 1. Genes involved in the endothelial system

Gene symbol	Gene name	Chr	Physical position ± 5,000 bp	SNPs	Function[a]
EDN2	Endothelin 2	1	(41944446, 41950344)	1	Induces vasoconstriction, principally through EDNRA stimulation[2]
DDAH1	Dimethylarginine dimethylamino-hydrolase 1	1	(85784168, 86044046)	90	Participates in NO generation by regulating cellular concentrations of methylarginines, which in turn inhibit NO synthase activity[3]
VCAM1	Vascular cell adhesion molecule 1	1	(101185196, 101204601)	5	Involved in leukocyte–endothelial cell adhesion and signal transduction[1]
SELE	Selectin E	1	(169691781, 169703220)	21	Mediates adhesion and transmigration of leukocytes to vascular endothelium[4]
EDNRA	Endothelin receptor type A	4	(148402069, 148466106)	25	Participates in stimulation of cytokine release and endothelial growth factors[5]
MEF2C	Myocyte enhancer factor 2C	5	(88014058, 88199922)	31	**Contributes to vascular endothelial growth factor expression in endothelial cells**[6]
EDN1	Endothelin 1	6	(12290529, 12297427)	13	Acts through its receptor stimulation, endothelin receptor type A (EDNRA) and endothelin receptor type B (EDNRB)[7]
SERPINE 1	Serpin peptidase inhibitor, clade E	7	(100770379, 100782547)	2	Contributes to cardiac ventricular remodeling by migration of inflammatory cells and attenuation of extracellular matrix degradation[8]
NOS3	Nitric oxide synthase 3, endothelial cell	7	(150688144, 150711687)	8	Mediates the conversion of L-arginine in NO[9]
VWF	von Willebrand factor	12	(6058040, 6233836,)	64	Marker of endothelial damage[10]
EDNRB	Endothelin receptor type B	13	(78469616, 78493903)	10	Participates in the control of vascular tone by stimulation of vascular smooth muscle cell receptors[11]
CYBA	Cytochrome b-245, alpha polypeptide	16	(88709697, 88717457)	1	Participates in the activation and stabilization of NADPH–oxidase[12]
TGFB1	Transforming growth factor, beta 1	19	(41836812, 41859831)	1	Regulates proliferation, differentiation, adhesion, migration, and other functions of the endothelial cell[13]
COL18A1	Collagen, type XVIII, alpha 1	21	(46825097, 46933634)	20	COL18A1 deficiency is associated with vascular endothelial cell damage and its degradation results in the generation of endostatin, a potent vasodilator[14]

Abbreviations: Chr, chromosome; NO, nitric oxide; SNPs, single nucleotide polymorphisms.
[a] References for gene function correspond with those found in the Supplementary References.

in the Supplementary Materials. Genetic data, genotyped as part of the Affymetrix platform (Affymetrix 6.0, Santa Clara, CA) and using SNPlex assays (Applied Biosystems, Carlsbad, CA) based on oligonucleotide ligation assay for capillary electrophoresis on an automated DNA sequencer (ABI 3700 DNA Analyzer), were available for 368 single nucleotide polymorphisms (SNPs) from the 14 candidate genes and their 5,000 base-pair flanking regions. After standard quality control procedures, 75 SNPs with an minor allele frequency (MAF) < 1% and 1 SNP with a genotyping call rate < 85% were excluded, leaving a total of 292 SNPs for the analysis. Supplementary Table S1 provides descriptive information and quality control parameters for these SNPs.

Statistical analysis

The percent or means of baseline and intervention variables were calculated for the 1,906 GenSalt feeding study participants. Additive associations between single SNPs and BP responses to each dietary sodium intervention were assessed using a mixed linear regression model to account for the nonindependence of family members. Age, sex, body mass index, room temperature during blood pressure measurement, and study site were adjusted in multivariable analyses. To adjust for multiple comparisons, the false discovery rate Q value was calculated for all SNPs.[18] Statistical significance was determined by $Q < 0.05$. For significant SNPs, the mean effect size and 95% confidence interval (CI) was estimated according to genotype. Because of the known role of estrogen in the activation of endothelial system components and observed sex differences in salt sensitivity,[10,19] we examined genotype–sex interactions in an additional analysis. For those interactions that were significant after adjustment for multiple testing, we estimated the mean effect size and 95% CI according to sex and genotype. SAS statistical software version 9.2 was used for the analysis (SAS Institute, Cary, NC). We used Haploview software version 4.2 (http://www.broadinstitute.org/haploview) to estimate linkage disequilibrium, defined by the pairwise r^2 value, between SNPs.[20]

RESULTS

Characteristics of 1,906 GenSalt intervention participants are shown in Table 2. SBP, DBP, and MAP changed

Table 2. Characteristics of 1,906 GenSalt dietary intervention participants

Variable	Mean ± SD or percentage	Median (interquartile range)
Age, years	38.7 ± 9.6	39.0 (33.0–46.0)
Men, %	53.0	
BMI, kg/m^2	23.3 ± 3.2	22.9 (21.1–25.2)
SBP, mm Hg		
Baseline	116.9 ± 14.2	115.8 (106.4–127.1)
Response to low-sodium intake	−5.5 ± 7.0*	−4.4 (−8.9 to −1.3)
Response to high-sodium intake	4.9 ± 6.0*	4.7 (0.6–8.2)
DBP, mm Hg		
Baseline	73.7 ± 10.3	73.3 (66.7–80.7)
Response to low-sodium intake	−2.8 ± 5.5*	−2.7 (−5.6 to 0.4)
Response to high-sodium intake	1.9 ± 5.4*	1.8 (−1.6 to 5.3)
MAP, mm Hg		
Baseline	88.1 ± 10.9	87.7 (80.0–95.4)
Response to low-sodium intake	−3.7 ± 5.3*	−3.3 (−6.6 to −0.6)
Response to high-sodium intake	2.9 ± 5.0*	2.7 (−0.4 to 5.9)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.
*$P < 0.0001$ when compared with no blood pressure change during sodium interventions.

significantly in response to the dietary sodium interventions, with mean decreases of 6 mm Hg, 3 mm Hg, and 4 mm Hg, respectively, in response to low-sodium intake and increases of 5 mm Hg, 2 mm Hg, and 3 mm Hg in response to high-sodium intake.

Figure 1 presents the association between each SNP and absolute SBP, DBP, and MAP responses to the low- (Figure 1a) and high-sodium (Figure 1b) interventions. After adjustment for multiple testing, *DDAH1* marker rs11161637 (MAF = 26%) was associated with SBP ($P = 2.00 \times 10^{-4}$; $Q = 0.05$) and MAP (P value $= 1.83 \times 10^{-4}$; $Q = 0.02$) responses to low-sodium intake. This marker explained 2.1% of the variation in each of these traits. *VWF* marker rs2239153 (MAF = 39%) was associated with DBP ($P = 1.22 \times 10^{-4}$; $Q = 0.03$) and MAP ($P = 4.44 \times 10^{-5}$; $Q = 0.01$) responses to low-sodium intake, explaining 1.1% and 0.9% of the variation in these traits, respectively. *COL18A1* SNP rs2838944 (MAF = 7%) was associated with SBP (P value $= 1.41 \times 10^{-4}$; $Q = 0.04$) and MAP ($P = 1.55 \times 10^{-4}$; $Q = 0.04$) responses to high-sodium intake, explaining 0.6% and 0.5% of their respective variances.

Mean BP responses and 95% CIs to the dietary sodium interventions according to *DDAH1* rs11161637, *VWF* rs2239153 and *COL18A1* rs2838944 genotypes are shown in Table 3. The magnitude of SBP and MAP responses to low-sodium intervention decreased significantly with the number of G alleles of *DDAH1* marker rs11161637. Although not significant after adjustment for multiple testing, similar trends were observed for DBP response to low-sodium intake ($P = 0.002$) and SBP, DBP, and MAP responses to high-sodium intake ($P = 0.006$, 0.005, and 0.001, respectively). In addition, DBP and MAP responses to low-sodium intake increased in magnitude with each copy of the *VWF* rs2239153 C allele. Although findings did not achieve statistical significance after correction for multiple testing, similar trends were observed for the association of rs2239153 with the other BP phenotypes ($P = 9 \times 10^{-4}$ for SBP response to low-sodium intervention; and $P = 0.001$, 0.004, and 7×10^{-4}, respectively, for SBP, DBP, and MAP responses to the high-sodium intervention). Finally, DBP and MAP responses to high-sodium intake decreased with each copy of the *COL18A1* rs2838944 A allele. A similar but nonsignificant trend was observed for SBP response to high-sodium intake ($P = 0.01$).

Figure 2 presents the P values for the tests of genotype–sex interactions on SBP, DBP, and MAP responses to the low- (Figure 2a) and high-sodium (Figure 2b) interventions. After adjustment for multiple testing, an interaction between *DDAH1* marker rs11161637 and sex was identified for SBP responses to low-sodium intake ($P = 2 \times 10^{-4}$; $Q = 0.05$). Examination of BP responses according to genotype and sex showed that the strong association in men ($P = 1.63 \times 10^{-7}$; $Q = 4.85 \times 10^{-5}$) was likely driving the association observed in the overall analysis (Table 4). In addition, 3 independent loci ($r^2 < 0.80$), which included 10 genetic variants, within the *SELE* gene displayed significant interactions with sex on DBP and MAP responses to low-sodium intervention ($P = 1.00 \times 10^{-3}$ to 1.00×10^{-4}). Among men, the minor alleles of highly correlated SELE markers rs5356, rs3917430, rs3917428, rs5368 (MAFs = 0.27–0.32) were associated with attenuated BP responses to the low-sodium intervention, with no associations observed in women. In contrast, the minor alleles of correlated markers rs3917436, rs3917423, rs3917406, and rs932307 were associated with increased BP responses to the low-sodium intervention among men (MAFs = 0.43–0.49), with no association among women. Finally, among correlated markers rs1534904 and rs3917412

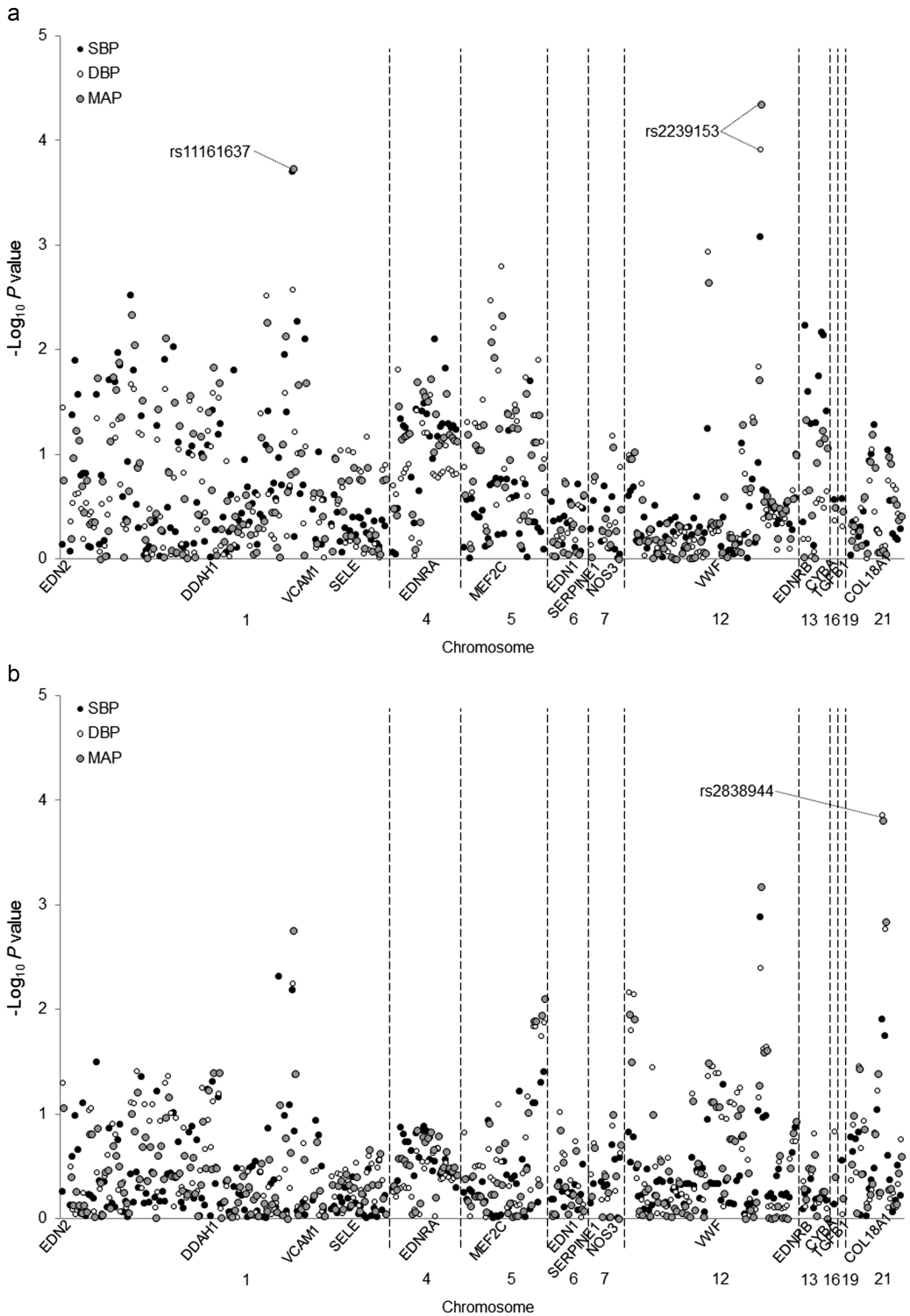

Figure 1. Log *P* values for the association between 292 single nucleotide polymorphisms in 14 candidate genes and systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) responses to low- (**a**) and high-sodium (**b**) interventions. Labeled single nucleotide polymporphisms had $Q < 0.05$. SNPs.

(MAF = 0.26 and 0.28, respectively), DBP and MAP responses to low-sodium intake tended to increase in men and decrease in women with each copy of the minor allele (Table 4).

DISCUSSION

This study identified several novel genetic variants in the endothelial system that may have important influences

Table 3. Blood pressure responses to dietary sodium interventions according to *DDAH1*, *VWF*, and *COL18A1* genotypes

HGNC symbol	Genotype		No.	Response to low-sodium intervention (95% CI)	*P*	*Q*	Response to high-sodium intervention (95% CI)	*P*	*Q*
Systolic blood pressure									
DDAH1	rs11161637	A/A	1021	−6.20 (−6.70 to −5.70)	0.0002	0.05	4.98 (4.56–5.40)	0.006	0.66
		A/G	732	−5.38 (−5.87 to −4.88)			4.04 (3.60–4.48)		
		G/G	128	−4.02 (−5.33 to −2.70)			4.38 (3.29–5.47)		
VWF	rs2239153	T/T	681	−5.12 (−5.65 to −4.60)	0.0009	0.13	4.15 (3.68–4.62)	0.001	0.39
		T/C	821	−6.06 (−6.61 to −5.52)			4.62 (4.19–5.05)		
		C/C	275	−6.54 (−7.40 to −5.68)			5.57 (4.82–6.32)		
COL18A1	rs2838944	G/G	1605	−5.73 (−6.14 to −5.33)	0.90	0.94	4.69 (4.35–5.02)	0.01	0.94
		G/A	263	−5.69 (−6.55 to −4.83)			3.89 (3.19–4.60)		
		A/A	9	−7.21 (−13.36 to −1.05)			2.00 (−0.50–4.49)		
Diastolic blood pressure									
DDAH1	rs11161637	A/A	1021	−3.01 (−3.43 to −2.60)	0.002	0.16	1.97 (1.61–2.32)	0.005	0.27
		A/G	732	−2.46 (−2.87 to −2.05)			1.28 (0.88–1.69)		
		G/G	128	−1.66 (−2.64 to −0.68)			1.17 (0.21–2.13)		
VWF	rs2239153	T/T	681	−2.13 (−2.55 to −1.72)	0.0001	0.03	1.32 (0.89–1.74)	0.004	0.24
		T/C	821	−3.09 (−3.54 to −2.64)			1.82 (1.43–2.20)		
		C/C	275	−3.38 (−4.08 to −2.67)			2.34 (1.71–2.96)		
COL18A1	rs2838944	G/G	1605	−2.70 (−3.05 to −2.36)	0.78	0.89	1.83 (1.52–2.14)	0.0001	0.04
		G/A	263	−2.70 (−3.39 to −2.02)			0.65 (0.00 –1.29)		
		A/A	9	−4.16 (−7.30 to −1.02)			−1.03 (−3.45 to 1.38)		
Mean arterial pressure									
DDAH1	rs11161637	A/A	1021	−4.08 (−4.47 to −3.69)	0.0002	0.02	2.97 (2.63 to 3.31)	0.001	0.13
		A/G	732	−3.43 (−3.83 to −3.04)			2.20 (1.83–2.57)		
		G/G	128	−2.45 (−3.42 to −1.48)			2.24 (1.35–3.12)		
VWF	rs2239153	T/T	681	−3.13 (−3.54 to −2.73)	4.4×10^{-5}	0.01	2.26 (1.87–2.66)	0.0007	0.09
		T/C	821	−4.08 (−4.51 to −3.65)			2.75 (2.40–3.10)		
		C/C	275	−4.43 (−5.11 to −3.76)			3.41 (2.83–4.00)		
COL18A1	rs2838944	G/G	1605	−3.72 (−4.04 to −3.40)	0.82	0.97	2.78 (2.50–3.07)	0.0002	0.04
		G/A	263	−3.70 (−4.37 to −3.03)			1.72 (1.13–2.31)		
		A/A	9	−5.16 (−9.12 to −1.20)			−0.04 (−1.81 to 1.72)		

Abbreviations: CI, confidence interval; COL18A1, collagen, type XVIII, alpha 1; DDAH1, dimethylarginine dimethylaminohydrolase 1; HGNC, Human Genome Nomenclature Committee; VWF, von Willebrand factor.

on BP salt sensitivity. The number of copies of the G allele of rs11161637 in the *DDAH1* gene was associated with decreased SBP and MAP responses to low-sodium intake. Examination of genotype–sex interaction revealed that these findings were likely driven by the strong associations observed in men. In addition, the C allele of *VWF* marker rs2239153 was related to increased DBP and MAP responses to low-sodium interventions in the overall analysis, whereas the *COL18A1* rs2838944 A variant was related to attenuated DBP and MAP responses to high-sodium intake. Further, genotype–sex interactions were also observed for 3 independent loci within the *SELE* gene. These findings could have important public health and clinical implications. Compared with common variants that have been reported previously for other BP-related traits, variants identified in our main analysis each explained a relatively large proportion of the variation in the BP salt-sensitivity phenotypes (ranging 0.5%–2.1%). These results highlight the potential utility of examining intermediate phenotypes in genomic study. Furthermore, by providing strong evidence of genotype–sex interactions, our findings suggest a genomic explanation for observed sex differences in this complex trait.

Encoding one of the major endothelium-derived vasoactive mediators, the *DDAH1* gene is implicated in BP salt sensitivity because of its influence on NO production through the regulation of asymmetrical dimethylarginine (ADMA).[21] ADMA,

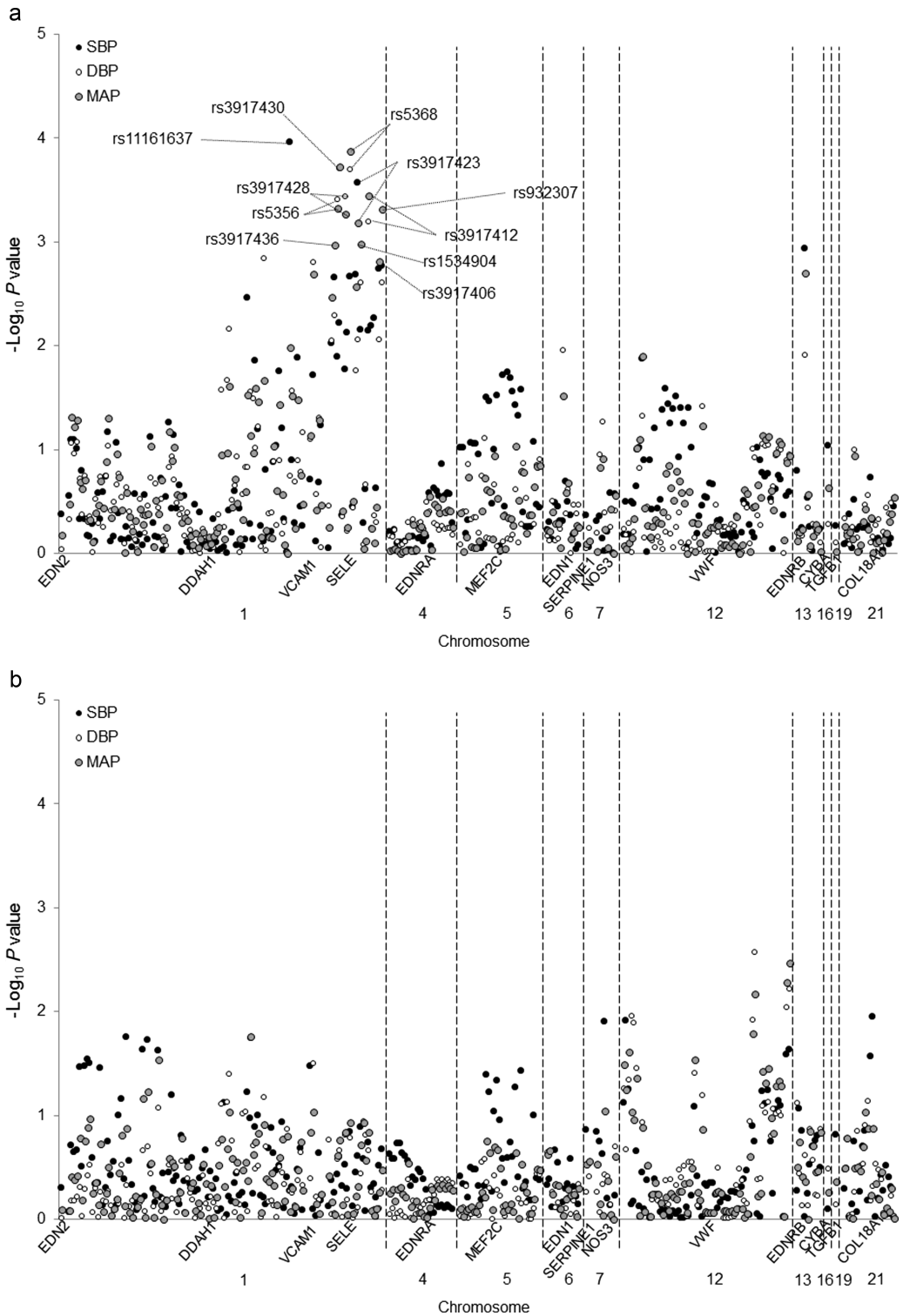

Figure 2. Log *P* values for the genotype–sex interactions of 292 single nucleotide polymorphisms in 14 candidate genes and systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) responses to low- (**a**) and high-sodium (**b**) interventions. Labeled SNPs had $Q < 0.05$.

which has been shown to increase after salt loading, is inversely associated with NO synthesis and BP.[22–24] DDAH1 metabolizes ADMA to L-citrulline and dimethylamine, playing a key role in the determination of in vivo ADMA concentration.[25] Although previous studies have not implicated *DDAH1* gene variants in the pathogenesis of salt sensitivity, *DDAH1* variants have been associated with ADMA concentrations and the increased risk of important BP-related traits, including

Table 4. Blood pressure responses to the dietary sodium interventions according to sex and genotypes

			Blood pressure response to low−sodium intervention					Blood pressure response to high−sodium intervention				
			Men		Women			Men		Women		
Gene	Genotype		Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]	Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]
Systolic blood pressure												
DDAH1	rs11161637	AA	−6.32 (−6.96 to −5.68)	1.72×10^{-7}	−5.77 (−6.53 to −5.01)	0.97	0.0001[b]	4.75 (4.22–5.27)	0.02	5.17 (4.52–5.83)	0.19	0.54
		AG	−4.78 (−5.40 to −4.17)		−5.79 (−6.61 to −4.98)			3.74 (3.14–4.34)		4.42 (3.77–5.07)		
		GG	−2.28 (−3.78 to −0.79)		−5.79 (−7.88 to −3.70)			3.91 (2.62–5.21)		4.93 (3.36–6.51)		
SELE	rs3917436	GG	−4.70 (−5.47 to −3.93)	0.004	−6.03 (−6.97 to −5.08)	0.13	0.002	3.98 (3.34–4.62)	0.64	4.90 (4.13–5.67)	0.71	0.57
		GA	−5.57 (−6.19 to −4.95)		−5.94 (−6.72 to −5.15)			4.65 (4.11–5.18)		4.92 (4.29–5.54)		
		AA	−6.59 (−7.62 to −5.57)		−4.89 (−5.97 to −3.80)			4.04 (3.22–4.86)		4.64 (3.70–5.58)		
	rs5356	TT	−5.84 (−6.48 to −5.20)	0.06	−5.43 (−6.21 to −4.65)	0.23	0.01	4.36 (3.87–4.87)	0.35	4.90 (4.26–5.53)	0.87	0.38
		TC	−5.11 (−5.75 to −4.47)		−6.28 (−7.13 to −5.44)			4.43 (3.84–5.02)		4.73 (4.07–5.39)		
		CC	−4.68 (−6.28 to −3.08)		−5.57 (−7.44 to −3.69)			3.11 (1.59–4.64)		5.45 (3.90–7.00)		
	rs3917430	CC	−5.92 (−6.59 to −5.24)	0.06	−5.18 (−5.97 to −4.39)	0.08	0.006	4.42 (3.90–4.95)	0.33	4.84 (4.20–5.48)	0.64	0.78
		CG	−5.15 (−5.77 to −4.53)		−6.46 (−7.29 to −5.64)			4.36 (3.81–4.90)		4.76 (4.12–5.40)		
		GG	−4.73 (−6.31 to −3.16)		−5.65 (−7.24 to −4.05)			3.60 (2.27–4.93)		5.41 (3.91–6.92)		
	rs3917428	GG	−5.80 (−6.44 to −5.16)	0.07	−5.40 (−6.17 to −4.63)	0.26	0.78	4.36 (3.87–4.86)	0.32	4.84 (4.22–5.46)	0.79	0.30
		GA	−5.22 (−5.86 to −4.57)		−6.37 (−7.23 to −5.23)			4.46 (3.86–5.06)		4.83 (4.16–5.50)		
		AA	−4.38 (−6.03 to −2.73)		−5.21 (−7.09 to −3.33)			2.98 (1.47–4.49)		5.20 (3.56–6.83)		
	rs5368	CC	−5.93 (−6.58 to −5.27)	0.01	−5.36 (−6.16 to −4.56)	0.11	0.59	4.44 (3.92–4.97)	0.14	4.85 (4.19–5.51)	0.65	0.14
		CT	−5.18 (−5.87 to −4.49)		−6.40 (−7.33 to −5.48)			4.30 (3.67–4.93)		4.74 (4.00–5.49)		
		TT	−3.59 (−5.38 to −1.80)		−5.81 (−7.96 to −3.66)			2.72 (0.99–4.45)		5.81 (3.92–7.70)		
	rs3917423	CC	−4.72 (−5.56 to −3.88)	0.002	−6.10 (−7.11 to −5.08)	0.05	0.0003[b]	3.87 (3.15–4.59)	0.45	5.09 (4.27–5.92)	0.33	0.25
		CT	−5.29 (−5.91 to −4.67)		−6.09 (−6.85 to −5.33)			4.58 (4.06–5.11)		4.90 (4.28–5.53)		
		TT	−6.64 (−7.49 to −5.78)		−4.81 (−5.78 to −3.85)			4.24 (3.51–4.97)		4.54 (3.73–5.35)		
	rs1534904	GG	−5.00 (−5.60 to −4.41)	0.02	−5.86 (−6.64 to −5.09)	0.22	0.007	4.04 (3.52–4.56)	0.25	4.93 (4.29–5.66)	0.34	0.13
		GT	−5.85 (−6.53 to −5.17)		−5.96 (−6.79 to −5.12)			4.69 (4.10–5.29)		4.91 (4.25–5.57)		
		TT	−6.53 (−8.13 to −4.93)		−4.16 (−5.65 to −2.68)			4.18 (3.10–5.25)		3.91 (2.55–5.27)		
	rs3917412	GG	−5.14 (−5.74 to −4.54)	0.04	−5.93 (−6.69 to −5.18)	0.13	0.78	4.11 (3.60–4.61)	0.27	4.90 (4.28–5.52)	0.44	0.18
		GA	−5.70 (−6.36 to −5.04)		−5.86 (−6.70 to −5.02)			4.60 (4.00–5.20)		4.95 (4.28–5.62)		
		AA	−6.96 (−8.76 to −5.16)		−3.97 (−5.46 to −2.48)			4.42 (3.18–5.65)		3.81 (2.26–5.37)		
	rs3917406	CC	−4.69 (−5.54 to −3.83)	0.01	−5.85 (−6.89 to −4.81)	0.07	0.002	3.72 (2.97–4.46)	0.37	5.03 (4.15–5.90)	0.56	0.30

Gene	Genotype		Blood pressure response to low-sodium intervention					Blood pressure response to high-sodium intervention				
			Men		Women			Men		Women		
			Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]	Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]
		CT	−5.50 (−6.14 to −4.85)		−6.00 (−6.79 to −5.21)			4.52 (3.95–5.09)		4.95 (4.27–5.64)		
		TT	−6.47 (−7.49 to −5.44)		−4.52 (−5.52 to −3.53)			4.12 (3.33–4.92)		4.65 (3.75–5.56)		
	rs932307	AA	−4.71 (−5.54 to −3.88)	0.005	−5.96 (−7.00 to −4.92)	0.08	0.002	3.58 (2.89–4.26)	0.14	4.88 (4.05–5.71)	0.58	0.22
		AG	−5.63 (−6.29 to −4.96)		−6.15 (−6.96 to −5.34)			4.69 (4.14–5.24)		4.89 (4.25–5.54)		
		GG	−6.52 (−7.48 to −5.57)		−4.72 (−5.76 to −3.69)			4.24 (3.42–5.06)		4.54 (3.68–5.41)		
Diastolic blood pressure												
DDAH1	rs11161637	AA	−2.76 (−3.13 to −2.20)	0.002	−3.02 (−3.60 to −2.44)	0.27	0.18	1.44 (0.97–1.90)	0.09	2.56 (2.01–3.11)	0.01	0.54
		AG	−1.94 (−2.49 to −1.38)		−2.74 (−3.38 to −2.09)			0.91 (0.32–1.49)		1.69 (1.07–2.31)		
		GG	−0.86 (−2.05 to 0.34)		−2.26 (−3.87 to −0.64)			0.68 (−0.51 to 1.86)		1.54 (0.10–2.99)		
SELE	rs3917436	GG	−1.83 (−2.47 to −1.20)	0.007	−3.25 (−3.94 to −2.55)	0.23	0.005	1.30 (0.72–1.89)	0.52	2.35 (1.68–3.01)	0.81	0.88
		GA	−2.30 (−2.82 to −1.78)		−2.61 (−3.23 to −1.99)			1.20 (0.71–1.68)		1.95 (1.37–2.54)		
		AA	−3.35 (−4.22 to −2.48)		−2.76 (−3.62 to −1.90)			0.98 (0.16–1.79)		2.33 (1.47–3.19)		
	rs5356	TT	−2.90 (−3.44 to −2.35)	0.0002	−2.65 (−3.26 to −2.03)	0.24	0.0004[b]	1.35 (0.88–1.83)	0.11	2.17 (1.57–2.76)	0.98	0.26
		TC	−1.90 (−2.47 to −1.33)		−3.10 (−3.75 to −2.45)			1.16 (0.59–1.73)		2.12 (1.52–2.72)		
		CC	−0.58 (−1.89 to 0.74)		−3.07 (−4.47 to −1.67)			0.10 (−1.04 to 1.25)		2.23 (0.97–3.50)		
	rs3917430	CC	−2.96 (−3.54 to −2.39)	0.0005	−2.56 (−3.19 to −1.94)	0.08	0.0002[b]	1.35 (0.84–1.86)	0.28	2.15 (1.54–2.75)	0.62	0.96
		CG	−1.95 (−2.50 to −1.39)		−3.04 (−3.68 to −2.40)			1.11 (0.56–1.65)		2.02 (1.44–2.60)		
		GG	−1.08 (−2.17 to 0.02)		−3.49 (−4.69 to −2.28)			0.79 (−0.15 to 1.73)		2.76 (1.49–4.03)		
	rs3917428	GG	−2.89 (−3.43 to −2.35)	0.0002	−2.62 (−3.22 to −2.01)	0.22	0.0004[b]	1.37 (0.89–1.85)	0.09	2.10 (1.52–2.67)	0.80	0.15
		GA	−1.92 (−2.49 to −1.35)		−3.18 (−3.83 to −2.52)			1.14 (0.57–1.71)		2.22 (1.60–2.83)		
		AA	−0.57 (−1.87 to 0.73)		−2.87 (−4.22 to −1.52)			0.09 (−1.03 to 1.21)		2.15 (0.90–3.40)		
	rs5368	CC	−3.03 (−3.57 to −2.49)	0.0003	−2.73 (−3.35 to −2.11)	0.12	0.18	1.37 (0.85–1.90)	0.21	2.21 (1.60–2.82)	0.68	0.17
		CT	−2.10 (−2.72 to −1.48)		−3.36 (−4.06 to −2.67)			1.26 (0.67–1.85)		2.25 (1.58–2.92)		
		TT	−0.21 (−1.74 to 1.31)		−3.39 (−5.04 to −1.73)			0.14 (−1.12 to 1.39)		2.68 (1.18–4.18)		
	rs3917423	CC	−1.73 (−2.42 to −1.04)	0.004	−3.02 (−3.75 to −2.28)	0.52	0.009	1.08 (0.46–1.69)	0.97	2.36 (1.64–3.07)	0.70	0.77
		CT	−2.20 (−2.74 to −1.67)		−2.85 (−3.45 to −2.24)			1.29 (0.80–1.79)		2.04 (1.45–2.62)		
		TT	−3.21 (−3.97 to −2.46)		−2.71 (−3.51 to −1.91)			1.08 (0.38–1.78)		2.17 (1.41–2.93)		
	rs1534904	GG	−1.97 (−2.48 to −1.45)	0.05	−3.15 (−3.72 to −2.57)	0.02	0.002	1.05 (0.59–1.51)	0.74	2.29 (1.72–2.86)	0.43	0.56
		GT	−2.72 (−3.30 to −2.15)		−2.67 (−3.34 to −2.01)			1.44 (0.90–1.98)		1.97 (1.34–2.61)		
		TT	−2.59 (−3.66 to −1..52)		−1.92 (−3.00 to −0.84)			0.77 (−0.43 to 1.96)		2.05 (0.83–3.27)		

(Continued)

Table 4. Continued

Gene	Genotype		Blood pressure response to low−sodium intervention					Blood pressure response to high−sodium intervention				
			Men		Women			Men		Women		
			Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]	Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]
	rs3917412	GG	−2.01 (−2.51 to −1.51)	0.06	−3.26 (−3.82 to −2.70)	0.003	0.0006[b]	1.13 (0.67–1.59)	0.80	2.37 (1.82–2.92)	0.17	0.22
		GA	−2.71 (−3.30 to −2.11)		−2.51 (−3.19 to −1.83)			1.28 (0.73–1.84)		1.90 (1.25–2.54)		
		AA	−2.69 (−3.90 to −1.47)		−1.69 (−2.85 to −0.52)			1.09 (−0.17 to 2.36)		1.78 (0.38–3.18)		
	rs3917406	CC	−1.95 (−2.64 to −1.25)	0.007	−3.27 (−4.07 to −2.46)	0.39	0.009	1.28 (0.64–1.92)	0.66	2.60 (1.81–3.39)	0.64	0.79
		CT	−2.05 (−2.61 to −1.48)		−2.88 (−3.54 to −2.22)			1.16 (0.64–1.68)		2.12 (1.49–2.75)		
		TT	−3.53 (−4.41 to −2.65)		−2.82 (−3.68 to −1.96)			1.06 (0.27–1.86)		2.38 (1.54–3.21)		
	rs932307	AA	−1.63 (−2.31 to −0.95)	0.002	−3.12 (−3.91 to −2.34)	0.34	0.003	0.91 (0.31–1.52)	0.58	2.33 (1.57–3.08)	0.68	0.53
		AG	−2.34 (−2.90 to −1.77)		−2.64 (−3.27 to −2.00)			1.26 (0.76–1.76)		1.99 (1.40–2.58)		
		GG	−3.38 (−4.22 to −2.53)		−2.66 (−3.49 to −1.82)			1.14 (0.35–1.93)		2.13 (1.34–2.92)		
Mean arterial pressure												
DDAH1	rs11161637	AA	−3.95 (−4.47 to −3.44)	1.19×10^{-5}	−3.94 (−4.49 to −3.38)	0.47	0.008	2.54 (2.12–2.97)	0.03	3.43 (2.90–3.97)	0.02	0.84
		AG	−2.89 (−3.40 to −2.38)		−3.76 (−4.38 to −3.15)			1.85 (1.33–2.37)		2.60 (2.04–3.16)		
		GG	−1.33 (−2.53 to −0.13)		−3.45 (−5.00 to −1.89)			1.74 (0.64–2.84)		2.68 (1.44–3.93)		
SELE	rs3917436	GG	−2.79 (−3.40 to −2.17)	0.002	−4.18 (−4.85 to −3.50)	0.13	0.001[b]	2.20 (1.66–2.73)	0.79	3.20 (2.57–3.84)	0.74	0.89
		GA	−3.39 (−3.88 to −2.91)		−3.72 (−4.32 to −3.13)			2.35 (1.91–2.79)		2.94 (2.40–3.47)		
		AA	−4.44 (−5.26 to −3.61)		−3.47 (−4.30 to −2.64)			2.00 (1.28–2.72)		3.10 (2.31–3.88)		
	rs5356	TT	−3.88 (−4.39 to −3.37)	0.0009	−3.58 (−4.18 to −2.98)	0.18	0.0005[b]	2.35 (1.93–2.78)	0.14	3.08 (2.52–3.63)	0.98	0.48
		TC	−2.97 (−3.50 to −2.45)		−4.17 (−4.78 to −3.56)			2.25 (1.74–2.77)		2.99 (2.44–3.53)		
		CC	−1.96 (−3.23 to −0.68)		−3.90 (−5.32 to −2.48)			1.12 (−0.04 to 2.27)		3.29 (2.09–4.50)		
	rs3917430	CC	−3.95 (−4.50 to −3.40)	0.002	−3.44 (−4.04 to −2.83)	0.05	0.0002[b]	2.37 (1.92–2.82)	0.25	3.05 (2.49–3.61)	0.61	0.88
		CG	−3.02 (−3.52 to −2.51)		−4.18 (−4.79 to −3.58)			2.19 (1.71–2.68)		2.92 (2.39–3.46)		
		GG	−2.30 (−3.45 to −1.15)		−4.20 (−5.39 to −3.00)			1.72 (0.76–2.68)		3.63 (2.40–4.87)		
	rs3917428	GG	−3.86 (−4.37 to −3.35)	0.001	−3.55 (−4.14 to −2.96)	0.18	0.0005[b]	2.37 (1.94–2.79)	0.11	3.01 (2.48–3.55)	0.78	0.15
		GA	−3.02 (−3.56 to −2.49)		−4.25 (−4.86 to −3.63)			2.25 (1.74–2.77)		3.08 (2.51–3.65)		
		AA	−1.85 (−3.12 to −0.58)		−3.64 (−5.02 to −2.27)			1.06 (−0.06 to 2.18)		3.17 (1.95–4.38)		
	rs5368	CC	−4.00 (−4.52 to −3.48)	0.0004	−3.61 (−4.22 to −3.00)	0.08	0.0001[b]	2.39 (1.94–2.85)	0.15	3.09 (2.51–3.66)	0.66	0.12
		CT	−3.13 (−3.70 to −2.56)		−4.38 (−5.05 to −3.71)			2.28 (1.74–2.82)		3.09 (2.51–3.66)		
		TT	−1.35 (−2.80 to 0.10)		−4.19 (−5.86 to −2.51)			1.00 (−0.30 to 2.29)		3.08 (2.44–3.71)		
	rs3917423	CC	−2.73 (−3.39 to −2.06)	0.001	−4.05 (−4.77 to −3.32)	0.18	0.0007[b]	2.01 (1.43–2.59)	0.75	3.28 (2.60–3.95)	0.48	0.49
		CT	−3.24 (−3.73 to −2.75)		−3.93 (−4.50 to −3.36)			2.39 (1.95–2.83)		2.99 (2.45–3.53)		

Gene	Genotype		Blood pressure response to low−sodium intervention					Blood pressure response to high−sodium intervention				
			Men		Women			Men		Women		
			Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]	Absolute change, mm Hg (95% CI)	*P*	Absolute change, mm Hg (95% CI)	*P*	Interaction *P*[a]
		TT	−4.36 (−5.06 to −3.65)		−3.41 (−4.17 to −2.65)			2.13 (1.50–2.76)		2.96 (2.26–3.65)		
	rs1534904	GG	−2.98 (−3.47 to −2.50)	0.02	−4.06 (−4.61 to −3.50)	0.04	0.001[b]	2.05 (1.62–2.47)	0.48	3.17 (2.63–3.71)	0.33	0.19
		GT	−3.77 (−4.30 to −3.24)		−3.77 (−4.41 to −3.13)			2.53 (2.04–3.02)		2.95 (2.37–3.52)		
		TT	−3.92 (−5.05 to −2.78)		−2.68 (−3.77 to −1.59)			1.90 (0.91–2.89)		2.67 (1.57–3.77)		
	rs3917412	GG	−3.06 (−3.53 to −2.59)	0.03	−4.15 (−4.69 to −3.62)	0.007	0.0004[b]	2.12 (1.70–2.54)	0.53	3.21 (2.69–3.73)	0.19	0.14
		GA	−3.71 (−4.25 to −3.17)		−3.63 (−4.29 to −2.97)			2.39 (1.89–2.89)		2.91 (2.32–3.50)		
		AA	−4.12 (−5.41 to −2.84)		−2.46 (−3.59 to −1.33)			2.20 (1.12–3.29)		2.47 (1.21–3.73)		
	rs3917406	CC	−2.86 (−3.52 to −2.19)	0.004	−4.13 (−4.89 to −3.37)	0.16	0.002[b]	2.10 (1.49–2.70)	0.97	3.40 (2.67–4.13)	0.60	0.56
		CT	−3.21 (−3.73 to −2.69)		−3.92 (−4.55 to −3.29)			2.28 (1.81–2.76)		3.05 (2.47–3.64)		
		TT	−4.51 (−5.36 to −3.66)		−3.39 (−4.19 to −2.59)			2.08 (1.39–2.78)		3.15 (2.41–3.89)		
	rs932307	AA	−2.66 (−3.31 to −2.01)	0.0008	−4.07 (−4.81 to −3.32)	0.14	0.0005[b]	1.80 (1.25–2.35)	0.32	3.18 (2.49–3.87)	0.60	0.34
		AG	−3.44 (−3.89 to −2.90)		−3.81 (−4.43 to −3.19)			2.40 (1.95–2.86)		2.95 (2.39–3.50)		
		GG	−4.43 (−5.23 to −3.63)		−3.35 (−4.15 to −2.55)			2.17 (1.46–2.88)		2.94 (2.22–3.65)		

Abbreviations: CI, confidence interval; COL18A1, collagen, type XVIII, alpha 1; DDAH1, dimethylarginine dimethylaminohydrolase 1; HGNC, Human Genome Nomenclature Committee; VWF, von Willebrand factor.

[a]*P* value for genotype–sex interaction.

[b]False discovery rate $Q < 0.05$.

chronic kidney disease, CVD, and thrombotic stroke.[26–28] The minor G allele of novel marker rs11161637, which lies in an intronic region of the *DDAH1* gene, was associated with decreased BP salt sensitivity in this study. This association was likely driven by the very strong association observed in men. Interestingly, Caplin and colleagues also noted a potential DDAH1–sex interaction in their analysis of plasma ADMA levels.[28] Because there is little evidence for regulatory action or conservation of rs11161637 across species, it is unlikely that it is causally associated with salt sensitivity. It is more plausible that the association reflects linkage disequilibrium with a functional but still undiscovered variant. Although we await replication and functional study to elucidate the true nature of the observed relationship, the results provide promising evidence for a role of the *DDAH1* gene in salt sensitivity of BP.

VWF is a largely endothelium-derived glycoprotein that is released into the circulation by damaged endothelial cells, promoting coagulation and platelet activation.[29] In this study, we observed a significant, positive association between the novel *VWF* rs2239153 variant and BP responses to sodium intake. Although we are the first to identify such an association, Ferri and colleagues showed that plasma levels of the VWF glycoprotein were significantly elevated among those with salt-sensitive hypertension compared with those with salt-resistant hypertension.[30] Furthermore, *VWF* gene polymorphisms have been associated with hypertension in past studies,[31,32] making it a logical candidate for genetic study of salt sensitivity. Marker rs2239153 represents a common, intronic SNP in the *VWF* gene with unknown functional effects. Future replication studies are needed to validate the observed association, whereas sequencing and functional studies will be required to pinpoint the true causal variant underlying this relationship.

COL18A1 encodes a potent antiangiogenic protein,[33] with its deficiency related to altered matrix remodeling, enhanced inflammatory response, and vascular endothelial cell damage.[34] Further, the degradation of *COL18A1* results in the generation of endostatin, which has been implicated in BP regulation because of its vasorelaxing effect.[35,36] Despite physiological evidence for a role of *COL18A1* in BP, to the knowledge of the authors, there have been no studies examining the association between *COL18A1* gene variants and BP-related phenotypes. In this study, we identified an inverse dose–allele relationship between the intronic *COL18A*1 rs2838944 A variant and BP responses to the dietary sodium intervention, demonstrating a potentially important influence of *COL18A1* on BP salt sensitivity.

We also identified 3 independent loci within the *SELE* gene that interacted with sex to influence BP salt sensitivity. Encoding a component of the selectin family of cell adhesion molecules, *SELE* is expressed in cytokine-stimulated endothelial cells and is thought to be involved in the pathogenesis of atherosclerosis.[37,38] Although not previously associated with BP salt sensitivity, other studies have reported a role for *SELE* in BP regulation and hypertension.[37,38] In addition, significant SELE–sex interactions on hypertension were reported in a separate study of Chinese participants.[37] Although some follow-up work is warranted, these findings highlight the importance of considering gene–environment interaction in the context of BP salt sensitivity.

To date, GenSalt is the largest dietary intervention study to examine the association between genetic variants in the endothelial system and BP response to dietary sodium intervention. Furthermore, study attributes, including the recruitment of all Han Chinese participants, should make the analysis robust to population stratification. Participation in the dietary intervention was high, and compliance, as assessed by urinary excretion of sodium and potassium, was excellent. In addition, stringent quality control procedures were employed during the BP measurements, collection of other study variables, conduction of the dietary interventions, genotyping, and marker data cleaning. Compared with previous reports of common BP-associated variants, the SNPs identified in this study explained a relatively large proportion of the variation in the BP salt-sensitivity phenotypes.[39] There are several potential explanations for these findings. As an intermediate BP phenotype, genetic heterogeneity may be reduced, decreasing the total phenotypic variance due to genomic factors. In addition, the study participants were similar with respect to lifestyle and environmental risk factors. These study attributes, along with the controlled dietary intake of sodium, decreased phenotypic variance due to environmental factors. Moreover, the multiple BP readings obtained on multiple days reduced the measurement errors, decreasing phenotypic variance due to random error. Finally, because of the "winner's curse," it is also possible that these findings represent an overestimate of the true proportion of variation explained by these SNPs. Therefore, caution is warranted in generalizing these findings beyond that of the current sample. Because our research was conducted in a Han Chinese population, the findings may not be generalizable to populations with distinct linkage disequilibrium structure. Finally, although the Affymetrix 6.0 platform generally provides good genomic coverage of common polymorphisms in the Han Chinese population (approximately 75%),[3] limited genotype data were available for the *EDN2*, *CYBA*, and *TGFB1* genes (see Supplementary Table S1). Therefore, future research to examine the association between common variants in these genes and BP salt sensitivity is still needed.

Our study is the first to associate endothelial system genes *DDAH1, VWF*, *COL18A1*, and *SELE* with BP salt sensitivity. Despite these promising results, further follow-up work is needed. Replication studies will be necessary to validate the novel associations reported here. Furthermore, sequencing and functional studies to pinpoint the causal variants underlying these relationships are warranted.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org/).

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DISCLOSURE

The authors declared no conflict of interest.

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