CYP4A11 T8590C polymorphism, salt-sensitive hypertension, and renal blood flow

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Abstract

Objective and methods—A loss-of-function cytosine (C) for thymidine (T) transition at nucleotide 8590 of *CYP4A11* has been associated with increased blood pressure in humans. We tested the hypothesis that *CYP4A11* T8590C genotype is associated with salt sensitivity in the International Hypertensive Pathotype cohort.

Results—*CYP4A11* T8590C genotype was associated with hypertension in whites. Among normotensive individuals, *CYP4A11* T8590C genotype was associated with mean arterial pressure (MAP) during both high and low salt diets, such that there was no relationship between genotype and salt sensitivity of blood pressure. Among hypertensive individuals, *CYP4A11* T8590C genotype did not associate with MAP during high salt intake, whereas MAP decreased with increasing number of C alleles during salt restriction. Consequently, among hypertensive individuals, change in MAP with salt restriction was greatest in individuals homozygous for the C allele (-10.9 ± 9.9, -11.1 ± 12.3, and -18.8 ± 12.0 mmHg in TT, CT, and CC groups, respectively, $P = 0.02$). In both normotensive and hypertensive individuals, individuals homozygous for the C allele exhibited an attenuated increase in renal blood flow during high salt. *CYP4A11* genotype did not affect pressor responses to Angiotensin II in normotensive or hypertensive individuals.

Conclusion—The loss-of-function *CYP4A11* 8590C allele is associated with a diagnosis of hypertension and, in normotensive individuals, with higher blood pressure regardless of salt intake. Among hypertensive individuals, the C allele is associated with salt-sensitive blood pressure. Impaired renal vasodilation during high salt intake may contribute to salt sensitivity. Studies are needed to determine whether *CYP4A11* T8590C genotype predicts responses to medications that affect sodium homeostasis in hypertensive individuals.

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Keywords

blood pressure; *CYP4A11*; dietary salt intake; hypertension; renal blood flow; salt sensitivity

Introduction

Hypertension affects 74.5 million people in the United States and is estimated to contribute to 300 000 deaths per year [1]. Sixty percent of patients with hypertension have 'salt-sensitive' blood pressure (BP). Salt-sensitive hypertension is associated with an increased risk of cardiovascular events [2].

Studies in experimental models of hypertension implicate the P450 arachidonic acid monooxygenases in salt and water homeostasis. Epoxygenases CYP2C and CYP2J catalyze the conversion of arachidonic acid to epoxyeicosatrienoic acids (EETs), potent vasodilators and anti-inflammatory agonists, whereas the ω/ω-1 hydroxylases, CYP4A and CYP4F, catalyze the conversion of arachidonic acid to 20-hydroxyeicosatetraenoic acid (20-HETE) [3]. The 20-HETE metabolite can act in either a prohypertensive or antihypertensive manner dependent on its site-specific expression in the renal vasculature or tubule, respectively [4]. For example, 20-HETE promotes natriuresis by inhibiting tubular sodium transport [5,6]. 20-HETE causes vasoconstriction by inhibiting Ca^{2+}-sensitive K^+ channels [7] and enhances the effects of angiotensin (Ang) II and endothelin [8,9]. Opposing this vasoconstrictor effect, products of CYP4A induce expression of CYP2C and the formation of vasodilatory EETs in the kidney [10].

In the Dahl rat model, decreased urinary excretion of 20-HETE is associated with salt sensitivity and insulin resistance [11]. Genetic studies indicate that the ω/ω-1 hydroxylase CYP4A11 also regulates BP in humans. A loss-of-function *CYP4A11* variant (8590C allele) characterized by reduced 20-HETE synthase activity has been associated with BP or hypertension in European and African–American populations, suggesting that 20-HETE exerts an antihypertensive effect in humans [12–15]. Nevertheless, the mechanism through which the loss-of-function C allele confers risk of hypertension is not known.

Laffer *et al.* [16] found no relationship between *CYP4A11* T8590C genotype and salt or insulin sensitivity in a small study of 25 carefully phenotyped hypertensive individuals, but reported that the increase in urinary 20-HETE excretion in response to salt loading was diminished in salt-sensitive, insulin-resistant individuals with the C allele.

The current study tested the hypothesis that *CYP4A11* T8590C genotype influences BP response to salt loading and vasoreactivity in a large group of well phenotyped individuals in the International Hypertension Pathotype (HyperPATH) study.

Methods

Individuals and protocol

Three hundred and thirty-two hypertensive and 147 normotensive individuals who had DNA available were drawn from the HyperPATH cohort [17,18]. A description of this cohort and study has been previously reported. Individuals were recruited from the general population of the Brigham and Women's Hospital, Boston (*n* = 185); Hospital Broussais in France (*n* = 82); University of Utah (*n* = 134); Rome, Italy (*n* = 17); and Vanderbilt University (*n* = 61). The Institutional Review Board of each institution approved the study. All individuals gave written informed consent before enrollment and underwent a standardized protocol. Some characteristics of subsets of this population have been reported previously [17–19]. The

present analyses of associations between phenotypes and *CYP4A11* T8590C genotype are original, however.

All individuals had a screening history, physical and laboratory examination. Individuals with known or suspected secondary hypertension, diabetes, coronary artery disease, stroke, overt renal insufficiency (serum creatinine > 1.5 mg/dl), current tobacco or illicit drug use, alcohol intake more than 12 ounces per week, or other significant medical or psychiatric illnesses were excluded. Individuals with abnormal electrolytes or thyroid/liver function tests or ECG evidence of heart block, ischemia, or prior coronary events at the screening examination were excluded. Individuals were between ages 18 and 65 years and race was self-defined.

Hypertension was defined as seated DBP of at least 100 mmHg off antihypertensive medication, at least 90 mmHg with one medication, or treatment with at least two medications. Individuals with hypertension requiring more than four medications were excluded. Normotensive individuals, in addition to having BP less than 140/90 mmHg, reported no first-degree relatives diagnosed with hypertension before age 60. Individuals taking an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or mineralocorticoid receptor antagonist were transitioned to amlodipine 3 months prior to study to minimize interference with assessment of the renin–angiotensin–aldosterone system. If needed, hydrochlorothiazide was added to control BP. All antihypertensive medications were discontinued 3 weeks before study.

Individuals then completed two dietary phases, a 5–7 day course of high sodium (≥200 mmol/day) and 7 days of low sodium (10 mmol/day) diets. Each diet was isocaloric, contained 100 mmol/day potassium, 20 mmol/day calcium, and was caffeine and alcohol-free. Sodium balance was confirmed by measuring sodium and creatinine in a 24-h urine collection (≥ 150 mmol urinary sodium for high sodium and ≤ 30 mmol for low sodium). On the final day of each diet, individuals were admitted to the General Clinical Research Center (GCRC) and remained fasting and supine overnight. Hemodynamic and hormone measurements were made between 0800 and 1000 h. During infusion studies, BP was measured at 5-min intervals using an automated device (DINAMAP, Critikon, Tampa, Florida, USA).

On the last day of high salt and low salt intake, the pressor, renal vasoconstrictor, and aldosterone responses to Ang II amide (3 ng/kg per min for 45 min) were measured in 432 individuals during high (TT:CT:CC = 270 : 97 : 14) and/or low salt (TT:TC:CC = 297 : 111 : 11) intake. The clearance of para-aminohippurate, infused as a bolus followed by a constant infusion, was used to assess renal plasma flow, as previously described [20]. The pressor response to graded doses norepinephrine was also measured in 181 of these individuals (130 : 41 : 10, respectively) during high salt intake, as a control for Ang II subtype 1 receptor-specific vasoconstriction.

Genotyping

Methods of laboratory analysis have been reported previously [20,21]. DNA was extracted from peripheral leukocytes using standard procedures. Genotyping was performed for the single single nucleotide polymorphism (SNP) T8590C (rs1126742) as a single plex on a Sequenom iPlex chemistry platform (Sequenom Inc., San Diego, California, USA). The genotyping success rate was 95.6% and repeat genotyping for 10% of the SNPs demonstrated concordance with the original genotype call. Genotyping results conformed to Hardy–Weinberg expectations in the study population.

Statistical analysis

Data are presented as means ± SD unless otherwise stated. Frequencies were compared among genotype groups using χ^2-test or Fisher's exact test. Continuous variables were compared among genotype groups using one-way analysis of variance or Kruskal–Wallis test. Within genotype group, the effect of salt was assessed using a paired *t*-test or signed-rank test, as appropriate. The pressor responses to Ang II or norepinephrine were analyzed using general linear model in which the within-subject variable was pressor dose and the between-subject variables were genotype, sex, quartile of age, and quartile of BMI. Analyses were completed using SPSS Statistics version 17.0 (SPSS Inc., Chicago, Illinois, USA). A *P* value less than 0.05 was considered significant.

Results

Baseline characteristics

Baseline characteristics appear in Table 1. Sex, age, and BMI were balanced across *CYP4A11* T8590C genotype groups. The frequencies of the *CYP4A11* 8590 minor allele were similar to those previously reported for all racial groups. [12–15]. The frequency of the C allele was increased in black Americans compared with white Americans studied (29 versus 13%, *P* < 0.001). History of hypertension was associated with *CYP4A11* T8590C genotype in white individuals (TT:CT:CC = 83.1 : 16.1 : 0.8% in normotensive individuals versus 72.4 : 25.7 : 2.0% in hypertensive individuals, *P* = 0.02) but not in black individuals studied. During high salt intake, mean arterial pressure (MAP) was 100.6 ± 18.7 and 100.7 ± 15.8 mmHg mmHg in the white American TT and CT genotype groups, respectively, versus 107.0 ± 13.6 mmHg in the CC genotype group. MAP was 104.0 ± 17.1, 104.1 ± 16.4, and 111.3 ± 24.9 mmHg in black American TT, CT, and CC genotype groups, respectively. Because the relationship between BP and *CYP4A11* T8590C genotype trended in the same direction in blacks and whites in this study and in previous reports, [15] we grouped racial groups together for the remainder of the analyses. We also included the small number of Asian and individuals of other race to maximize power, although results of analyses were comparable if these individuals were excluded.

Relationship between *CYP4A11* T8590C genotype and blood pressure

Among normotensive individuals, *CYP4A11* T8590C genotype was associated with BP during both high and low salt intake (Table 2). In normotensive individuals, the difference in BP measured during low salt intake compared with that measured during high salt intake ($DMAP_{low-high}$) was similar among genotype groups (Fig. 1). Among hypertensive individuals, *CYP4A11* T8590C genotype did not statistically associate with MAP during high salt intake, whereas during low salt intake BP decreased as the number of C alleles increased. Thus, $\Delta MAP_{low-high}$ was significantly greater in individuals homozygous for the C allele (−10.9 ± 9.9, −11.1 ± 12.3, and −18.8 ± 12.0 mmHg in TT, CT, CC genotype groups, respectively, *P* = 0.02) among hypertensive individuals (Fig. 1). In addition, among hypertensive individuals, *CYP4A11* T8590C genotype was significantly associated with salt-sensitive hypertension, defined as a decrease in MAP from high to low salt of at least 10 mmHg. Specifically, the prevalence of salt sensitivity was 50.2, 47.2, and 81.8% in hypertensive TT, CT, and CC genotype groups (*P* = 0.03 for CC genotype versus the other two genotype groups). When this analysis was stratified by race, the pattern was similar in blacks and whites with a prevalence of salt sensitivity of 45.5, 50.0, and 100% in black hypertensive TT, CT, and CC genotype groups and 51.3, 44.1, and 66.7% in white hypertensive TT, CT, and CC genotype groups, respectively.

Relationship between *CYP4A11* T8590C genotype and renal blood flow

Twenty-four hour urine sodium excretion provided evidence of dietary compliance and was comparable among the three genotype groups in normotensive and hypertensive individuals (Tables 2 and 3). Aldosterone and plasma renin activity (PRA) were suppressed during high salt intake compared with low salt intake and comparable among genotype groups. Renal plasma flow was statistically similar among the genotype groups; however, *CYP4A11* T8590C genotype affected the relationship between salt intake and renal plasma flow (Tables 2 and 3, Fig. 2). Renal plasma flow was significantly greater during high salt intake compared with during low salt intake in TT normotensive individuals and in TT and TC hypertensive individuals, but this pattern was reversed in normotensive or hypertensive individuals homozygous for the C allele (Fig. 2).

CYP4A11 T8590C genotype and the pressor effects of Ang II and norepinephrine

Ang II significantly increased MAP during both high salt (Fig. 3) and low salt (not shown) conditions ($P < 0.001$ for effect of Ang II in either normotensive or hypertensive individuals), as previously described [22]. *CYP4A11* T8590C genotype did not affect the pressor response to Ang II in either normotensive or hypertensive individuals, regardless of salt intake (all $P > 0.05$ for genotype $\times$ Ang II interaction). *CYP4A11* genotype also did not affect the renal vasoconstrictor response to Ang II (shown for high salt in supplemental figure, http://links.lww.com/HJH/A112) or the aldosterone response to Ang II (shown for low salt in supplemental figure, http://links.lww.com/HJH/A112).

Norepinephrine also significantly increased MAP in normotensive and hypertensive individuals (Fig. 3). *CYP4A11* T8590C genotype did not affect the pressor response to norepinephrine in either normotensive or hypertensive individuals, regardless of salt intake salt intake ($P = 0.138$ for genotype $\times$ norepinephrine interaction, $P = 0.067$ for CT versus TT genotype).

Discussion

The loss-of-function *CYP4A11* 8590C allele has been associated with higher BP or a diagnosis of hypertension in population studies [12–15]. In this study, we confirm that the *CYP4A11* T8590C genotype is associated with hypertension, and with BP among normotensive individuals. We demonstrate for the first time that, among hypertensive individuals, homozygosity for the C allele is associated with salt-sensitive BP. We also report that homozygosity for the C allele is associated with relative renal vasoconstriction during high salt intake. Of note, we found no relationship between *CYP4A11* T8590C genotype and Ang II or norepinephrine-induced vasoconstriction.

These findings resemble observations in the Dahl salt-sensitive rat model of hypertension. *CYP4A* genotype segregates with salt-sensitive hypertension in this rodent model [11]. Decreased ω/ω-1 hydroxylase activity is associated with salt-sensitive hypertension, whereas induction of CYP4A increases pressure natriuresis in the Dahl salt-sensitive rat [23]. Conversely, pharmacological inhibition of 20-HETE production in the outer medulla of the kidney in Lewis rats renders them salt-sensitive [24].

Interestingly, we found that the relationship between *CYP4A11* T8590C genotype and salt sensitivity of BP differed in the normotensive and hypertensive individuals studied. Among normotensive individuals without a family history of hypertension, *CYP4A11* genotype was associated with BP and independent of salt intake. In hypertensive individuals, sensitivity of BP resulted from a greater decrease in BP during low salt intake with an increasing number of C alleles. This difference in salt-sensitivity between normotensive and hypertensive individuals resembles that described by Weinberger *et al.* [25], who reported that

normotensive and hypertensive individuals responded similarly to salt loading, but that hypertensive individual exhibited a greater decrease in BP during salt restriction. An important implication of this finding in the present study is that the relationship between *CYP4A11* T8590C genotype and BP in large epidemiological studies may depend on the population studied and on sodium intake.

It is important to note that although the *CYP4A11 CC* genotype was associated with salt-sensitive hypertension, approximately one-half of individuals in the hypertensive TT and CT genotype groups also had salt-sensitive BP. Likewise, the prevalence of salt-sensitive hypertension in the population [2] far exceeds the frequency of the CC genotype (3.3% of all hypertensive individual in this study). Recent studies suggest, however, that even rare variants can contribute substantially to common complex traits such as salt-sensitive BP [26].

20-HETE also inactivates calcium-sensitive potassium channels in vascular smooth muscle [7], causes renal vasoconstriction in rodent models, and enhances vascular reactivity to constrictors such as Ang II, endothelin, and norepinephrine [9,27,28]. We found no effect of *CYP4A11* T8590C genotype on the constrictor response to systemic Ang II or norepinephrine infusion. Instead, we found that renal plasma flow was not increased appropriately during salt loading in individuals homozygous for the C allele. Although 20-HETE acts as a vasoconstrictor, metabolites of CYP4A induce CYP2C and the renal formation of vasodilatory EETs in rodent models [10] Our data suggest that the predominant effect of the loss-of-function *CYP4A11* 8590C allele in humans is relative renal vasoconstriction, consistent with decreased formation of EETs.

Laffer *et al.* [16] previously reported an association between *CYP4A11* T8590C genotype and the aldoster-one-to-renin ratio in individuals carrying the C allele compared with those with the TT genotype. In the present study, aldosterone and PRA were appropriately suppressed during high salt intake in all groups, consistent with increased volume, but were not significantly different among the genotype groups. Although we too noted a somewhat higher aldosterone-to-renin ratio in homozygotes for the C allele during high salt intake, this was attributable to a trend toward decreased PRA in carriers of the C allele and was not significant.

A few limitations merit notation. The relatively small number of black individuals makes it impossible to draw conclusions regarding the relationship between *CYP4A11* T8590C genotype and hypertension in this group, although one other study has shown an association [15]. In addition, because 20-HETE and the EETs undergo oxidative degradation over time and because urine samples had been stored for several years, we did not assess the effect of salt loading or *CYP4A11* T8590C genotype on 20-HETE or EET excretion. Ward *et al.* [29] have reported previously that the C allele is associated with decreased urinary 20-HETE excretion. On the contrary, the ability to assess genotype–phenotype relationships in a large number of individuals who had been carefully phenotyped with respect to salt-sensitivity and vascular reactivity outweighs these limitations.

In conclusion, prior reports indicate an association of BP and hypertension with the loss-of-function variant 8590C of *CYP4A11* in humans. The present study confirms this finding and indicates that homozygosity for the C allele results in altered renal vascular dilation during high dietary salt intake. In addition, among hypertensive individuals, homozygosity for the C allele is associated with salt-sensitive BP. Studies are needed to determine whether treatment strategies that improve renal vascular function and/or that affect natriuresis have preferential benefit in hypertensive individuals who are homozygous for the *CYP4A11* 8590C allele.

Abbreviations

|	
20-HETE	20-hydroxyeicosatetraenoic acid
C allele	cytosine allele
CC genotype	homozygous for cytosine on each of two inherited alleles
CT genotype	heterozygous, with one cytosine and one thymidine allele
EETs	epoxyeicosatrienoic acids
HyperPATH	hypertension pathotype
MAP	mean arterial pressure
T allele	thymidine allele
TT genotype	homozygous for thymidine on each of two inherited alleles

Acknowledgments

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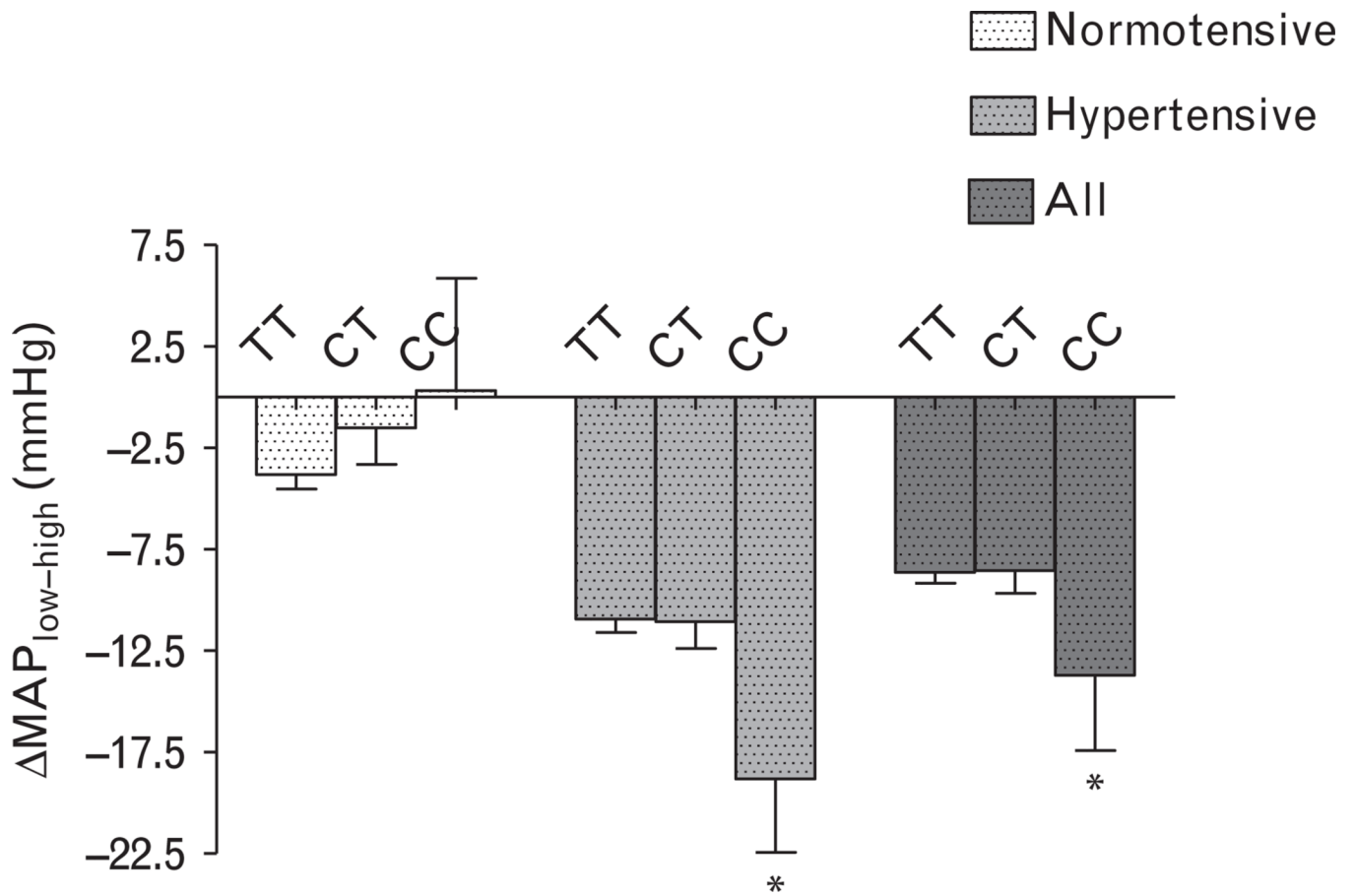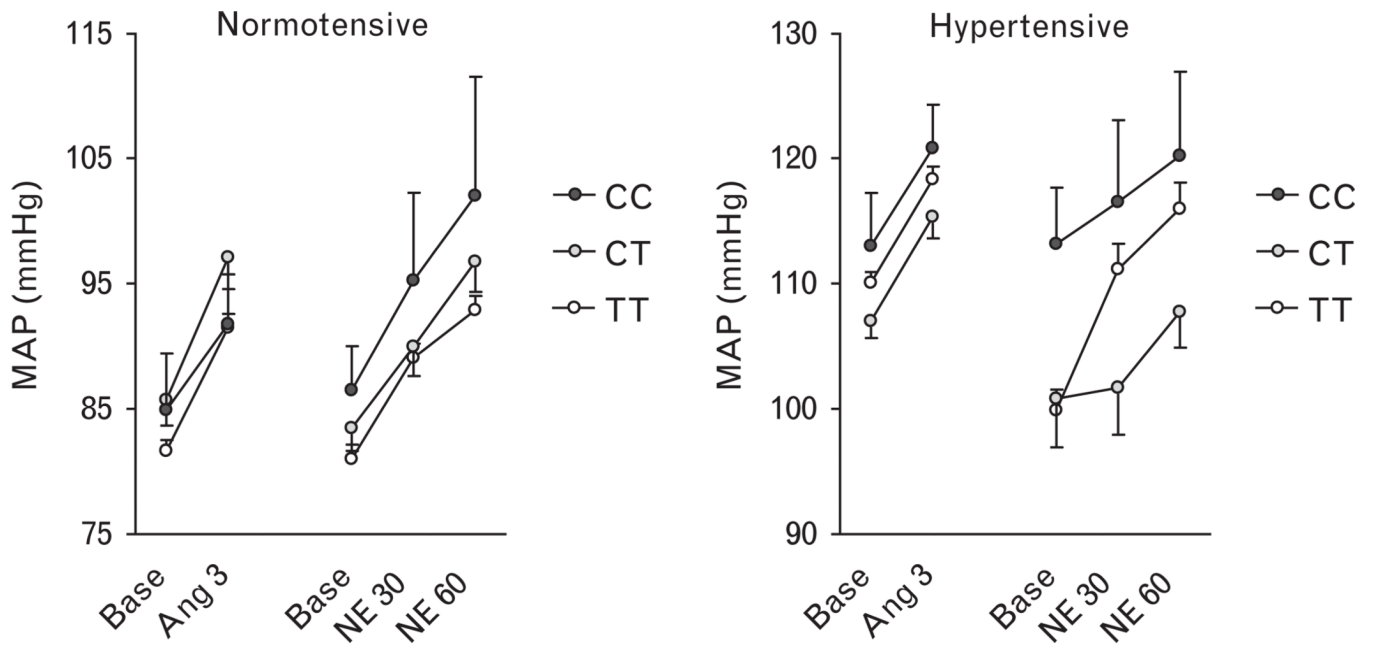
Fig. 1.
Relationship between *CYP4A11* T8590C genotype and change in mean arterial pressure (MAP) during low versus high salt intake. Data are presented as mean ± SEM. C indicates cytosine and T indicates thymidine. *P < 0.05 versus TT or CT genotype groups.
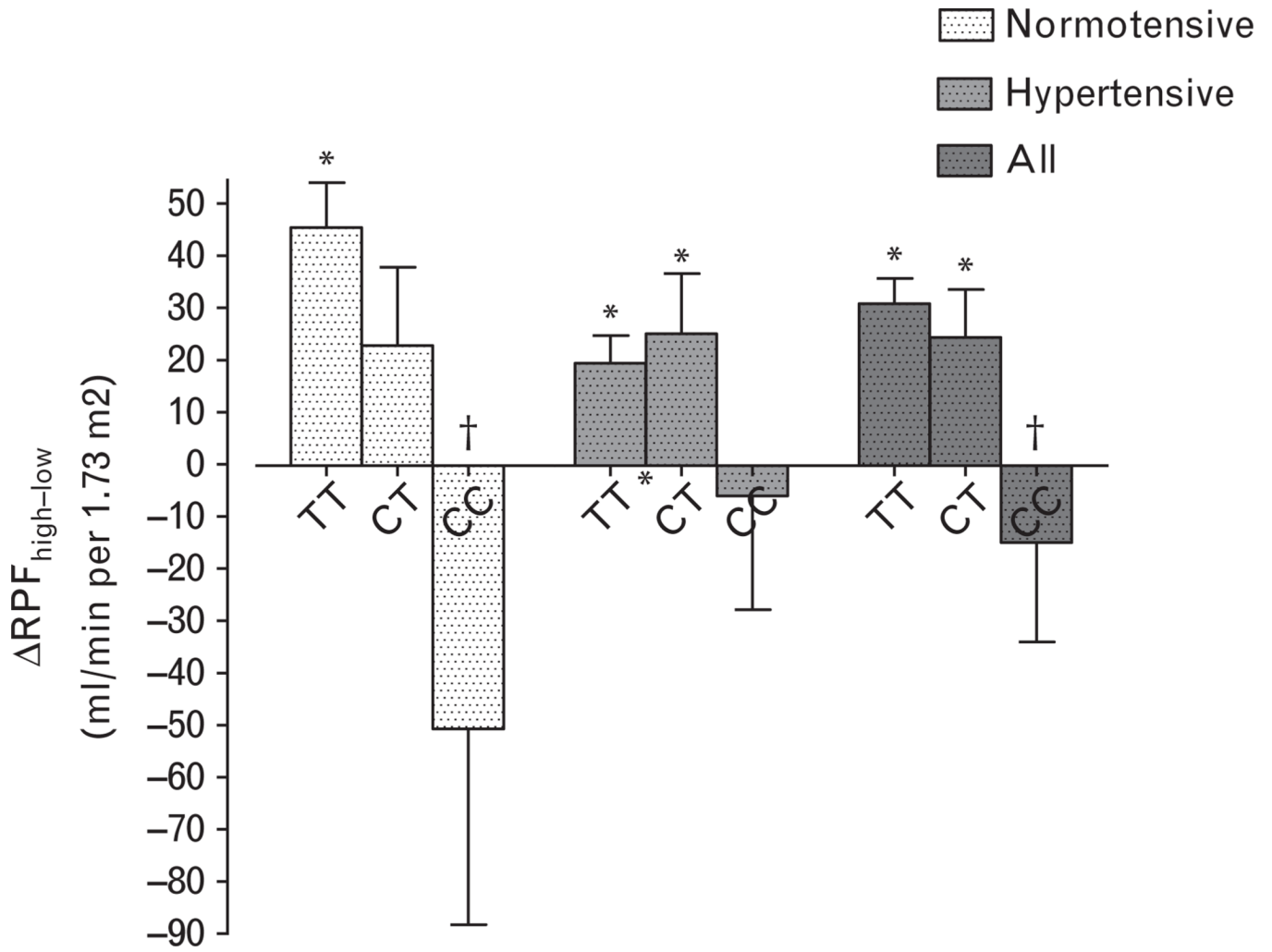
Fig. 2.
Relationship between *CYP4A11* T8590C genotype and change in renal plasma flow (ΔRPF) during high versus low salt intake. Data are presented as mean ± standard error of the mean. C indicates cytosine and T indicates thymidine. *$P < 0.05$ for the comparison of RPF during high salt versus during low salt. †$P < 0.05$ versus TT and CT genotype groups combined.

Fig. 3.
Relationship between *CYP4A11* T8590C genotype and the pressor response to intravenous angiotensin at a dose of 3 ng/min (Ang 3) or norepinephrine at doses of 30 and 60 µg/min (NE30 and NE60) during high salt (200 mmol/day) in normotensive (left panel) and hypertensive (right panel) individuals. Data are presented as mean ± SEM. C indicates cytosine and T indicates thymidine.

Table 1

Subject characteristics by *CYP4A11* T8590C genotype

Characteristic	TT (*n* = 336)	CT (*n* = 128)	CC (*n* = 15)	*P* value genotype
Race (white:black:Asian:other)	296:33:4:3	93:30:4:1	7:5:3:0	<0.001
Sex (M : F)	175:161	76:52	7:8	0.32
Age (years)	45.7 ± 10.5	45.5 ± 10.5	44.7 ± 11.8	0.92
BMI (kg/m^2)	27.4 ± 4.3	27.3 ± 4.0	27.8 ± 4.2	0.92

F, female; M, male.

Table 2

Normotensive individuals

	TT (*n* = 109)	CT (*n* = 34)	CC (*n* = 4)	*P* value genotype
SBP (mmHg)				
High salt	110.5 ± 12.3[*]	115.1 ± 12.2	118.8 ± 23.7	0.03
Low salt	106.6 ± 12.2	113.1 ± 12.8	113.3 ± 9.0	0.009
DBP (mmHg)				
High salt	66.2 ± 8.7[*]	67.5 ± 11.0	68.0 ± 1.2	0.45
Low salt	63.7 ± 7.9	66.3 ± 8.7	64.8 ± 8.0	0.16
MAP (mmHg)				
High salt	81.7 ± 9.4[*]	85.7 ± 12.3	84.9 ± 10.0	0.06
Low salt	77.7 ± 8.6	83.7 ± 10.4	85.3 ± 2.8	0.001
Heart rate (beats/min)				
High salt	58.9 ± 8.4[*]	60.5 ± 11.9	56.0 ± 5.3	0.74
Low salt	60.7 ± 8.7	61.2 ± 10.7	61.8 ± 7.3	0.73
24-h sodium (mmol/day)				
High salt	240.2 ± 77.9[*]	242.2 ± 77.9[*]	246.6 ± 118.9[*]	0.87
Low salt	10.1 ± 8.1	8.5 ± 7.7	12.2 ± 10.2	0.60
24-h potassium (mmol/day)				
High salt	77.0 ± 28.2	69.4 ± 24.5	51.7 ± 27.4	0.06
Low salt	72.4 ± 21.6	75.3 ± 24.4	80.6 ± 19.9	0.41
Plasma renin activity (ng/min per ml)				
High salt	0.40 ± 0.39[*]	0.37 ± 0.29[*]	0.22 ± 0.11[*]	0.55
Low salt	4.36 ± 4.46	4.22 ± 2.90	5.10 ± 4.13	0.95
Aldosterone (ng/dl)				
High salt	4.08 ± 3.22[*]	3.83 ± 2.00[*]	2.51 ± 0.03[*]	0.36
Low salt	19.24 ± 12.00	21.98 ± 12.57	19.98 ± 11.81	0.54
RPF (ml/min per 1.73m^2)				
High salt	601.4 ± 141.5[*]	573.5 ± 126.8	518.5 ± 53.0	0.24
Low salt	552.4 ± 134.2	544.3 ± 109.1	569.0 ± 106.1	0.89

MAP, mean arterial pressure; RPF, renal plasma flow.

[*] *P* < 0.05 versus low salt.

Table 3

Hypertensive individuals

	TT (n = 227)	CT (n = 94)	CC (n = 11)	P value genotype
SBP (mmHg)				
High salt	148.7 ± 20.8[*]	147.5 ± 19.7[*]	151.0 ± 18.9[*]	0.87
Low salt	133.7 ± 19.3	130.5 ± 20.2	123.9 ± 12.2	0.05
DBP (mmHg)				
High salt	89.6 ± 12.3[*]	86.2 ± 11.6[*]	91.2 ± 11.8[*]	0.13
Low salt	81.1 ± 11.7	77.5 ± 11.7	77.8 ± 9.4	0.02
MAP (mmHg)				
High salt	110.1 ± 14.0[*]	107.0 ± 13.2[*]	113.0 ± 14.5[*]	0.32
Low salt	99.4 ± 13.3	96.3 ± 13.7	94.2 ± 9.3	0.03
Heart rate (beats/min)				
High salt	65.4 ± 10.0	64.3 ± 10.6	62.3 ± 9.0	0.26
Low salt	66.2 ± 10.3	63.9 ± 10.1	63.7 ± 7.9	0.07
24-h sodium (mmol/day)				
High salt	221.5 ± 74.8[*]	226.7 ± 85.9[*]	225.6 ± 74.5[*]	0.62
Low salt	15.7 ± 11.7	15.9 ± 10.2	10.5 ± 8.3	0.62
24-h potassium (mmol/day)				
High salt	71.1 ± 25.2	66.6 ± 20.9	65.3 ± 23.8	0.12
Low salt	72.4 ± 20.0	71.4 ± 21.2	76.6 ± 23.9	0.92
Plasma renin activity (ng/min per ml)				
High salt	0.53 ± 0.57[*]	0.50 ± 0.53[*]	0.45 ± 0.30[*]	0.61
Low salt	2.93 ± 3.18	2.75 ± 2.19	3.49 ± 3.91	0.99
Aldosterone (ng/dl)				
High salt	5.56 ± 4.31[*]	5.45 ± 3.78[*]	4.67 ± 2.87[*]	0.59
Low salt	16.44 ± 11.50	17.02 ± 12.00	18.35 ± 10.00	0.55
RPF (ml/min per 1.73m^2)				
High salt	517.8 ± 102.9[*]	519.0 ± 117.2[*]	508.8 ± 90.1	0.93
Low salt	493.3 ± 104.3	497.7 ± 117.6	519.9 ± 101.1	0.55

MAP, mean arterial pressure; RPF, renal plasma flow.

[*] $P < 0.05$ versus low salt.