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ORIGINAL ARTICLE

A common polymorphism of *CYP4A11* is associated with blood pressure in a Chinese population

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Variants of the human *CYP4A11*, which belongs to the cytochrome P450, family 4, have been reported to be associated with hypertension in general populations. However, data in the Chinese population are limited. This study sought to assess the effect of *CYP4A11* on the prevalence of hypertension and blood pressure in a Chinese population. Three tagging single nucleotide polymorphisms, rs9332982, rs4660980 and rs3890011, were genotyped in 1734 community-based participants. Individuals with secondary hypertension were excluded. Sex-pooled and sex-specific analysis for genotype–phenotype association were both conducted. We found rs9332982 T allele was nominally associated with higher prevalence of hypertension in women after adjustment for covariates (OR: 1.38, 95%CI: 1.06–1.81, *P*=0.0183). The significance did not retain after Bonferroni correction. In blood pressure analysis restricted to normotensive individuals, rs4660980 was associated with both systolic (*β*=−3.17, *P*=0.0011) and diastolic blood pressure (*β*=−1.75, *P*=0.0010) in men. A common variant on *CYP4A11* was associated with blood pressure in a Chinese population. Future studies are needed to confirm our findings.
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INTRODUCTION

Essential hypertension is a major risk factor for cerebral, cardiac and renal events.[1,2] It is a late-onset, multifactorially determined pathological condition. The substantial heritability of blood pressure (BP) variability is supposed to facilitate the identification of responsible genes, which might shed light on the pathogenesis of the disease. To date, several variants have been identified by two genome-wide association studies to be associated with BP and hypertension.[3,4]

Human CYP4A11, which belongs to the cytochrome P450, family 4, catalyzes the formation of 20-hydroxyeicosatetraenoic acid (20-HETE) in the kidney. It is now clear that 20-HETE has both pro- and anti-hypertensive properties. In the renal and peripheral vasculature, 20-HETE is a potent vasoconstrictor that contributes to the autoregulation of renal-blood flow and renal vascular tone. It promotes calcium influx by depolarizing renal vascular smooth muscle cells secondary to blockade of K_{Ca} channels and by increasing the conductance of L-type Ca^{2+} channels. At the level of the renal tubule, 20-HETE inhibits sodium reabsorption, increases sodium excretion and opposes the development of hypertension. However, 20-HETE elevates vascular tone in the afferent arterioles and augments tubuloglomerular feedback responses, which would lower glomerular filtration rate, promote volume retention and elevate BP.[5] Given the role of 20-HETE in the regulation of BP, *CYP4A11* had gained much research interest. In 2005, Gainer *et al*[6] reported that a functional variant of *CYP4A11*, T8590C (rs1126742), was related to an increased prevalence of hypertension in two populations of European decent. And this association was supported by several subsequent studies in independent populations.[6–10] More recently, −845A/G (rs9332978), located in the promoter region of *CYP4A11*, was identified by Sugimoto *et al.*[11] to be a risk-conferring polymorphism in a Japanese population, strengthening the role for *CYP4A11* as a susceptible gene to hypertension.

However, these studies focused on certain variants that were either non-synonymous or located in the promoter region, whereas leaving most of the *CYP4A11* gene region unexamined. Besides, genetic association studies need to be replicated in different populations and whether *CYP4A11* variants had a role in modulating BP in Chinese remains unknown. By selecting tagging single nucleotide polymorphisms (SNPs), this study aimed to examine the association of *CYP4A11* variants with hypertension and BP in a Chinese population.

METHODS

Subjects

The subjects were selected from the Shanghai Diabetes Study,[12] a community-based epidemiological survey for diabetes. Briefly, the Huayang and Caoyang communities, two middle-income communities in Shanghai, were selected for the survey. The target population included residents over 40 years of age who

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had been living in Shanghai for more than 10 years. Individuals who suffered from secondary hypertension, cancer, severe disability or severe psychiatric disturbance were excluded. A total of 1734 unrelated individuals from Huayang and Caoyang communities were recruited in this study. Hypertension was defined as systolic BP (SBP) $\geqslant$140 mm Hg and/or diastolic blood pressure (DBP) $\geqslant$90 mm Hg, or the self report of disease affection. To fully exclude the confounding effect of diabetes on hypertension, only those subjects with normal glucose regulation (fasting plasma glucose $<6.1\,mmol\,l^{-1}$ and 2-h plasma glucose $<7.8\,mmol\,l^{-1}$ confirmed by a standard 75-g oral glucose tolerance test) were included into the final study cohort. The study protocol was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China. All participants gave informed consent before the study.

Clinical measurements

General anthropometric parameters including height and weight were measured in all subjects. Body mass index (BMI) was calculated as weight/height^2. BP measurements were taken three times using a sphygmomanometer in each participant while seated, after 5 min of rest. The averaged BP was used for subsequent analysis.

SNP selection and genotyping

On the Basis of data from HapMap Phase 3 Chinese data, we selected three tagging SNPs (rs9332982, rs4660980 and rs3890011) for genotyping using the Tagger software incorporated in Haploview (version 4.1) (see ref, 13). These three SNPs could capture all the SNPs with minor allele frequencies over 0.05 in the region from 6 kb upstream to 1 kb downstream of *CYP4A11* gene under the threshold of r^2=1. In addition, T8590C (rs1126742) was also genotyped, as this SNP had been reported to be associated with hypertension in different populations.

Genomic DNA was extracted from WBCs using a standard phenol–chloroform method. Genotyping was performed by primer extension of multiplex products with detection by matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy using a MassARRAY platform (MassARRAY Compact Analyzer; Sequenom, San Diego, CA, USA). The call rates for rs9332982, rs4660980 and rs3890011 were 98.2, 95.4 and 97.2%, respectively. The SNP rs1126742 was excluded from subsequent analysis because of genotyping failure. The average concordance rate based on 100 duplicate pairs for the three SNPs was 99%.

STATISTICAL ANALYSIS

Allele frequencies for each SNP were calculated by gene counting. The genotype frequency distribution for each variant was tested for Hardy–Weinberg equilibrium with a chi-square test in case and control groups separately. All the tests were conducted assuming an additive genetic model. The association between genotype and hypertension for each SNP was assessed using the Cochran–Armitage test for trend. The unconditional logistic regression analysis with adjustment for age, BMI and sex (when appropriate) was carried out to evaluate the effect of each variant on the prevalence of hypertension and odds ratios (ORs) with 95% confidence intervals (CIs) were presented. The multiple linear regression analysis was performed to examine the association between each SNP and BP. Age, BMI and sex (when appropriate) were included in the regression model as covariates. Pairwise linkage disequilibrium (LD) measures were calculated for all DNA samples using Haploview. Haplotype frequencies were estimated using an expectation maximization-based algorithm.[14] Haplotypes with a frequency of $<$0.01 were excluded. We used the Bonferroni method to adjust for multiple comparisons. As 9, 18 and 12 tests were performed in hypertension prevalence, BP and haplotype analysis, respectively, only those P values of $<$ 0.0055 (0.05/9), 0.0027 (0.05/18) and 0.0041 (0.05/12) were considered statistically significant. All statistical analyses were performed using SAS for Windows (version 8.0; SAS Institute Cary, NC, USA).

Table 1 Baseline characteristics of hypertensive and normotensive individuals

Parameters	*Hypertensive*	*Normotensive*	P
n	549	1185	
Gender, male/female	266/283	448/737	$<$0.0001
Age, years	61.34 ± 12.04	55.54 ± 12.04	$<$0.0001
BMI	24.83 ± 3.04	22.94 ± 2.81	$<$0.0001
Systolic pressure, mm Hg	146.12 ± 15.47	116.24 ± 11.68	$<$0.0001
Diastolic pressure, mm Hg	90.44 ± 8.68	74.15 ± 6.37	$<$0.0001

For continuous variables, mean ± SD is shown and for binary variables, the number of individuals is given.

For SNPs with minor allele frequency (MAF) $>$0.2 under an additive genetic model, our entire study cohort had over 80% power to detect a minimal OR of 1.29 for hypertension, and the control subgroup had over 80% power to detect a genetic effect of 1.6 and 0.9 mm Hg on SBP and DBP, respectively.

RESULTS

The baseline characteristics of the study population are described in Table 1. Of the entire 1734 subjects, 549 were hypertensive. The prevalence of hypertension for men and women was 37.25 and 27.75%, respectively. Individuals with hypertension were 5.8 years older and had a significantly higher BMI when compared with normotensive individuals. The MAFs for rs9332982, rs4660980 and rs3890011 were 18.2, 19.4 and 47.2%, respectively. All three SNPs conformed to Hardy–Weinberg equilibrium.

Table 2 shows the results of the association assessment between each polymorphism and hypertension. In total participants and in men, we failed to detect any association between the three SNPs and the prevalence of hypertension. In women, rs9332982 risk T allele was nominally associated with a higher prevalence of hypertension with adjustment for age and BMI (OR: 1.38, 95%CI: 1.06–1.81, P=0.0183). However, the P-value was not significant ($>$0.0055) after Bonferroni's correction.

Because the detailed information of the usage of anti-hypertensive agents was not available for the hypertensive subjects, we conducted the BP analysis only in the control group (Table 3). No evidence of association for the three SNPs with BP was observed in women. In total participants, rs4660980 showed a trend toward association with SBP (P=0.0104), although not significant. In the men subgroup, however, rs4660980 was significantly associated with both SBP (β=$-$3.19, P=0.0011) and DBP (β=$-$1.75, P=0.0010), even at the significance level of 0.0027 after Bonferroni's adjustment.

According to $|D'|$ and r^2, all three SNPs were in one block (Table 4). These SNPs formed four haplotypes with a frequency of $>$0.01 in our population (Table 5). No haplotype was differently distributed between hypertensive and normotensive subjects, either in the total group or in men. In women, the frequency of the T-T-C haplotype constructed by rs9332982, rs3890011 and rs4660980 was higher for the hypertensive group than for the control group (OR: 1.3179, 95% CI: 1.0296–1.6868, P=0.0282). However, the significance did not retain after correction for multiple testings.

DISCUSSION

In this study, we select three tagging SNPs for genotyping in 1734 unrelated Chinese subjects. The SNP rs4660980 was significantly associated with both SBP and DBP in normotensive men, even after Bonferroni's correction.

Table 2 Genotype and allele distributions in men and women stratified by the presence or absence of hypertension

	Total				*Men*				*Women*			
	HT	*NT*	P[a]	*ORs*[a]	*HT*	*NT*	P[a]	*OR*[a]	*HT*	*NT*	P[a]	*OR*[a]
rs9332982												
CC	358 (66.4%)	789 (67.8%)			183 (69.8%)	283 (64.6%)			175 (63.2%)	506 (69.8%)		
CT	158 (29.3%)	334 (28.7%)			70 (26.7%)	138 (31.5%)			88 (31.8%)	196 (27.0%)		
TT	23 (4.3%)	40 (3.5%)	0.1500	1.16 (0.95–1.41)	9 (3.5%)	17 (3.9%)	0.4815	0.90 (0.67–1.21)	14 (5.0%)	23 (3.2%)	0.0183	1.38 (1.06–1.81)
rs4660980												
TT	341 (64.7%)	730 (64.7%)			158 (61.5%)	282 (66.5%)			183 (67.8%)	448 (63.6%)		
TC	173 (32.8%)	353 (31.3%)			93 (36.2%)	131 (30.9%)			80 (29.6%)	222 (31.5%)		
CC	13 (2.5%)	45 (4.0%)	0.2145	0.88 (0.72–1.08)	6 (2.3%)	11 (2.8%)	0.5164	1.11 (0.81–1.51)	7 (2.6%)	34 (4.9%)	0.0312	0.74 (0.56–0.97)
rs3890011												
GG	151 (28.2%)	313 (27.2%)			81 (30.9%)	109 (25.1%)			70 (25.5%)	204 (28.5%)		
GC	263 (49.1%)	585 (50.9%)			120 (45.8%)	222 (51.2%)			143 (52.2%)	363 (50.8%)		
CC	122 (22.7%)	251 (21.9%)	0.9468	0.99 (0.85–1.17)	61 (23.3%)	103 (23.7%)	0.4565	0.92 (0.73–1.15)	61 (22.3%)	148 (20.7%)	0.6636	1.05 (0.84–1.31)

Abbreviations: HT, hypertensive; NT, normotensive; ORs, odds ratios.
[a]*P* values are adjusted for age and BMI as covariates.

Table 3 Association of the three SNPs on *CYP4A11* with blood pressure in normotensive individuals

		SBP			*DBP*		
SNPs		β	*SE*	P[a]	β	*SE*	P[a]
rs9332982	Total	0.39	0.59	0.5067	0.26	0.33	0.4367
	Men	0.46	0.91	0.6142	0.25	0.50	0.6188
	Women	0.32	0.77	0.6756	0.25	0.44	0.5625
rs4660980	Total	−1.47	0.57	0.0104	−0.49	0.33	0.1316
	Men	−3.19	0.97	0.0011	−1.75	0.53	0.0010
	Women	−0.68	0.71	0.3403	0.11	0.41	0.7949
rs3890011	Total	−0.77	0.46	0.0972	−0.19	0.26	0.4637
	Men	−1.43	0.73	0.0516	−0.73	0.40	0.0713
	Women	−0.41	0.59	0.4957	0.12	0.35	0.7248

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; SE, standard error; SNPs, single nucleotide polymorphisms.
[a]*P* values are adjusted for age, BMI and sex (when appropriate) as covariates.

Table 4 Pairwise linkage disequilibrium among the three SNPs

	|D′|		
r^2	*rs9332982*	*rs4660980*	*rs3890011*
rs9332982		0.97	0.99
rs4660980	0.05		0.99
rs3890011	0.24	0.27	

Abbreviation: SNPs, single nucleotide polymorphisms.
|*D*1 above diagonal and r^2 below diagonal.

The metabolism of arachidonic acid by cytochrome P450 (CYP) enzymes leads to the formation of various biologically active eicosanoids, such as hydroxyeicosatetraenoic acids, epoxyeicosatrienoic acids and dihydroxyeicosatrienoic acids.[15–17] These metabolites have a major role in the regulation of renal vascular tone, tubuloglomerular feedback and sodium transport. Of them, 20-HETE can exert an effect in a pro-hypertensive or anti-hypertensive manner depending on its expression at renovascular or tubular sites.[18,19]

One coding SNP, rs1126742 (T8590C), in exon 11 of *CYP4A11* was found to be associated with human BP and has been replicated in several populations.[6–10] The T to C substitution leads to an F to S replacement at amino-acid 434. Compared with F434 (wild type), the S434 replacement reduced by more than half the 20-HETE synthase activity of CYP4A11 (see ref. 6). Although the genotype data of rs1126742 were not available for our study samples, we have sequenced 115 individuals and found this SNP in tight LD with rs4660980 (D'=1, r^2=0.95) (ESM Table 1), which displayed a significant relation to BP in the current study. rs4660980 maps to intron 9 of *CYP4A11* without any known function. *In silico* analysis with SNP Function Portal (http://brainarray.mbni.med.umich.edu/Brainarray/Database/SearchSNP/snpfunc.aspx) shows that this SNP, including linked SNPs ($D' \geqslant 0.8$) registered on Hapmap, does not affect the splicing or transcription of *CYP4A11*. Thus, we believe that the real association arises from rs1126742 and our finding further supported the role for rs1126742 in the regulation of BP.

It is noteworthy that we used a stringent strategy (Bonferroni) to adjust for multiple comparisons. In spite of the low probability of type I error, some real association may also be underestimated. For instance, we observed in individual SNP test and haplotype analysis that rs9332982T allele was nominally correlated with a higher risk of developing hypertension. Interestingly, rs9332982 was in perfect LD (r^2=1) with rs9332978 according to HapMap HCB data. The latter SNP was recently reported by Sugimoto *et al.*[11] rs9332878 locates in the promoter region of *CYP4A11*. The G allele may decrease transcriptional activation of CYP4A11, thus leading to lower 20-HETE production in the kidney. Taken together, we suggest that studies with large sample size may be needed to clarify the effect of rs9332978 on BP in different populations.

One major limitation of this study resides in relatively low statistical power to detect a modest effect, especially in subgroup analyses (ESM tables 2, 3 and 4). For example, the power for rs9332982 (MAF 18%)

Table 5 Association between the haplotypes of *CYP4A11* and hypertension in women

	SNPs			*Frequency*			
Haplotypes	*rs9332982*	*rs4660980*	*rs3890011*	*HT*	*NT*	*OR (95% CI)*	P
1	C	T	G	0.52	0.542	0.9153 (0.7522–1.1136)	0.3745
2	C	C	C	0.177	0.207	0.8228 (0.6391–1.0592)	0.1290
3	T	T	C	0.209	0.167	1.3179 (1.0296–1.6868)	0.0282
4	C	T	C	0.094	0.083	1.1381 (0.8093–1.6004)	0.4601

Abbreviations: CI, confidence intervals; HT, hypertensive; NT, normotensive; ORs, odds ratios; SNPs, single nucleotide polymorphisms.

and rs4660980 (MAF 19%) to detect an OR of 1.3 in women assuming an additive model was 56 and 58%, respectively, and the power decreases in the men subgroup. The resulting statistical fluctuation may, at least partially, explain the discrepancy between men and women with respect to nominal association signals. Another limitation is the lack of data of serum or urinary 20-HETE, the measurement of which may give a hint to the functional relevance of susceptible SNPs in the modulation of BP.

In summary, rs4660980 was associated with both SBP and DBP in men. Given the tight LD between rs4660980 and rs1126742 (T8590C), this study provides further evidence for rs1126742 in the regulation of BP. Another SNP, rs9332982, showed a nominal association with hypertension prevalence in women, suggesting that the previous reported rs9332978, in perfect LD with rs9332982, may be worthy of investigation in the future.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)