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Original Article

Relationship between CYP17A1 Genetic Polymorphism and Essential Hypertension in a Chinese Population

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ABSTRACT: The relationship between CYP17A1 genetic polymorphisms and essential hypertension (EH) remains unclear. The aim of this study was to investigate the association of CYP17A1 genetic polymorphisms with EH in Han and Uighur populations in China. A Han population including 558 people (270 EH patients and 288 controls) and a Uighur population including 473 people (181 EH patients and 292 controls) were selected. Five single-nucleotide polymorphisms (SNPs) (rs4919686, rs1004467, rs4919687, rs10786712, and rs2486758) were genotyped using real-time PCR (TaqMan). In the Uighur population, for the total and the men, rs4919686, rs4919687 and rs10786712 were found to be associated with EH (rs4919686: P≤0.02, rs4919687: P≤0.002, rs10786712: P≤0.004, respectively). The difference remained statistically significant after the multivariate adjustment (all P<0.05). The overall distributions of the haplotypes established by SNP1–SNP3, SNP1–SNP4, SNP1–SNP3–SNP5 and SNP1–SNP4–SNP5 were significantly different between the EH patients and the control subjects (for the total: P=0.013, P=0.008, P=0.032, P=0.010, for men: P<0.001, P=0.001, P=0.010, P=0.00). In the Han population, for men, rs2486758 was found to be associated with EH in a recessive model (P=0.007); the significant difference was not retained after the adjustment for the covariates (date not shown). The A allele of rs4919686 could be a susceptible genetic marker, and the T allele of rs10786712 could be a protective genetic marker of EH. The AC genotype of rs4919686, the AG genotype of rs4919687 and the TT genotype of rs10786712 could be protective genetic markers of EH.

Key words: CYP17A1 gene, single nucleotide polymorphism, essential hypertension, case–control study

Essential hypertension (EH) affects one-fourth of adults worldwide, and this proportion is expected to increase to one-third by 2025 [1]. Hypertension is one of the most important risk factors for cardiovascular diseases, stroke, and end-stage renal disease and is the most important risk factor for morbidity and mortality [2-5]. Each year, approximately one-half of all cases of stroke and myocardial ischemia worldwide are caused by hypertension [6]. The etiology and pathogenesis of EH are likely to comprise a multifactorial disorder resulting from environmental and genetic factors and their interaction. Over the last decade, scientists have found many gene variants associated with EH [7-9], and twin studies have shown that variations in blood pressure have a heritability factor of approximately 50% [10].

The CYP17A1 gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases that catalyze many reactions involved in drug metabolism as well as the synthesis of cholesterol, steroids and other lipids, and they are responsible for the metabolism of xenobiotics and many endogenous substances whose metabolites have critical roles in the maintenance of cardiovascular health [11, 12]. Recently, several studies

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have indicated that CYP17A1 is associated with hypertension [13-16]. Genome-wide association studies (GWAS) could screen for the gene polymorphism loci associated with hypertension [17]. Tabara et al [18] performed a multiple regression analysis with possible covariates and showed that CYP17A1 was independently associated with blood pressure (BP) traits and hypertension. They confirmed that CYP17A1 independently determined BP traits and hypertension after adjusting for age, sex, body mass index (BMI), and drinking habits. In 2010, Liu et al [19] found that CYP17A1 gene rs1004467 was significantly associated with increased systolic blood pressure (SBP: P=0.005), diastolic blood pressure (DBP: P=0.01) and risk of hypertension (P=0.0009).

In humans, the CYP17A1 gene is located on chromosome 10q24.3, consisting of eight exons and seven introns, and is primarily expressed in the adrenal glands and gonads. The CYP17A1 gene produces the P450c17 protein, which is a key enzyme in the steroidogenic pathway that produces sex hormones. Some evidence has indicated that the levels of sex hormones could affect the development of cardiovascular and cerebrovascular diseases [20]. Sex hormones including estrogens protect against oxidative stress and are known to be vaso protective [21-23].

In this case–control study, we aimed to assess the association between the polymorphism of CYP17A1 and essential hypertension in a Chinese population.

MATERIAL AND METHODS

Ethical approval of the study protocol

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Xinjiang, China) and was conducted according to the standards of the Declaration of Helsinki. Written informed consent was obtained from each participant, including explicit permission for the DNA analyses and the collection of relevant clinical data.

Study population

We randomly recruited 270 Han patients (145 men, 125 women) and 181 Uighur patients (103 men, 78 women) with EH and 288 and 292 ethnically and geographically matched control group subjects. All the subjects attended the First Affiliated Hospital of Xinjiang Medical University from 2007 to 2013 as inpatients. All the patients presented with hypertension defined as having an SBP/DBP ≥140/90 mmHg [24], and the participants with hypertension had parents, siblings, or both with hypertension, were undergoing antihypertensive medication therapy or had been previously diagnosed with hypertension. In addition, we excluded any subjects with secondary hypertension, such as primary aldosteronism or kidney disease. Patients with multiple organ failure, a mental disorder, or chronic inflammatory disease were excluded from this study. The normotensive controls had no family history of hypertension, had never been treated with antihypertensive medications, and presented with SBP/DBP <120/80 mmHg; additionally, participants with coronary artery disease, multiple organ failure, or a mental disorder were excluded from this study.

Biochemical analyses

For the biochemical analyses, 5 ml of fasting venous blood was drawn by venipuncture from all the participants. The blood samples were collected and centrifuged at 4000 ×g for 5 min to separate the plasma content (including the plasma and blood cells). The genomic DNA was extracted using the standard phenol-chloroform method [25]. The DNA samples were stored at −80 °C for future analysis. For the analyses, the DNA was diluted to a 50-ng/μL concentration. The plasma concentrations of glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), creatinine (Cr) and uric acid (UA) were measured using standard methods in the Central Laboratory of First Affiliated Hospital of Xinjiang Medical University, as described previously [26-28].

Genotyping of the CYP17A1 gene

Using Haploview 4.2 software and the HapMap phase II database, five tag SNPs (SNP1: rs4919686, SNP2: rs1004467, SNP3: rs4919687, SNP4: rs10786712, SNP5: rs2486758) were obtained using a minor allele frequency (MAF) ≥0.05 and linkage disequilibrium patterns, with $r^2 \geq 0.8$ as the cut off. The genotyping was confirmed by the TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA). The TaqMan SNP Genotyping Assays were performed using Taq amplification.

Statistical analysis

The statistical analyses were performed using the SPSS 17.0 for Windows (SPSS Institute, Chicago, USA). Statistical significance was established as a P-value < 0.05. All the continuous variables (e.g., age, TC, TG, HDL-C, LDL-C, BMI) are presented as the means ± standard deviation (SD), and the difference between the EH and control groups was analyzed using an independent-sample T-test. All the classification variables (e.g., the frequencies of smoking, drinking, diabetes mellitus, and

CYP17A1 genotypes) and the Hardy-Weinberg equilibrium were analyzed using the $\chi 2$ test or Fisher's exact test, as appropriate. Logistic regression analyses with effect ratios (odds ratio [OR] and 95% CI) were used to assess the contribution of the major risk factors. The linkage disequilibrium (LD) analysis and haplotype-based case-control analysis were performed using the expectation maximization (EM) algorithm [29] and SHEsis software (www.analysis.bio-x.cn/SHEsisMain.htm). The pairwise linkage disequilibrium analysis was performed using five SNP pairs, and the frequency distribution of the haplotypes was calculated by performing a permutation test using the bootstrap method.

RESULTS

Characteristics of the study participants

As shown in Table 1, for the Han and Uighur populations, there was no significant difference in age between the EH patients and the control subjects, which indicated that the study was an age-matched case-control study. In the Han population, for the total subjects and women participants, the incidence of diabetes and the plasma concentration of uric acid (UA) were significantly higher in the EH subjects than in the controls; for the total subjects, the following values were significantly higher for the EH patients than for the control subjects: the incidence of drinking and the BMI; for the male subjects, the incidence of drinking and smoking were significantly higher in the EH subjects than in the controls; for the female subjects, the BMI and the plasma concentration of Cr were significant higher for the EH patients than for the control participants. In the Uighur population, for the total subjects, the incidence of diabetes, smoking, and drinking were significantly higher in the EH subjects than in the controls; for the male subjects, the incidence of smoking and drinking were significantly higher for the EH patients compared to the control subjects; for the female subjects, the plasma concentration of Cr was significantly higher for the EH patients than for the control participants.

Table 1. Demographic and clinical characteristics of study participants

	Han								
	total			men			women		
	EH	controls	P	EH	controls	P	EH	controls	P
Number (n)	270	288		145	157		125	131	
Age, mean (SD)	62.47(9.88)	61.52(10.03)	0.264	60.15(11.08)	60.19(11.19)	0.779	64.75(7.71)	63.12(8.2)	0.103
Diabetes (%)	35(13.0)	19(6.6)	0.011	17(11.7)	15(9.6)	0.540	18(14.4)	4(3.1)	0.001
Smoking (%)	41(15.2)	29(10.1)	0.068	41(28.3)	28(17.8)	0.031	0	1(0.9)	0.328
Drinking (%)	36(13.3)	23(8.0)	0.040	36(25.1)	23(14.6)	0.018	0	0	1
BMI, mean (SD)	26.35(3.66)	25.44(3.31)	0.002	26.94(3.85)	26.04(3.15)	0.106	25.69(3.33)	24.73(3.37)	0.023
Glu(mmol/L)	5.79(2.17)	5.49(1.56)	0.062	5.97(2.21)	5.53(1.59)	0.077	5.61(1.48)	5.44(1.53)	0.525
TG(mmol/L)	2.05(1.96)	1.90(1.44)	0.326	2.19(2.17)	2.09(1.68)	0.651	1.89(1.69)	1.69(1.06)	0.250
TC(mmol/L)	4.30(1.36)	4.30(0.997)	0.969	4.14(1.11)	4.16(0.97)	0.855	4.51(0.95)	4.46(1.00)	0.703
HDL(mmol/L)	1.11(0.32)	1.12(0.32)	0.605	1.03(0.28)	1.04(0.30)	0.651	1.20(0.33)	1.21(0.32)	0.771
LDL(mmol/L)	2.53(0.94)	2.55(0.83)	0.826	2.48(1.02)	2.53(0.82)	0.615	2.85(2.25)	2.57(0.84)	0.303
UA(umol/L)	330.82(91.34)	312.89(75.23)	0.012	355.18(79.27)	340.57(73.76)	0.101	303.59(96.77)	279.32(62.43)	0.019
Cr(umol/L)	73.60(17.45)	71.15(17.80)	0.104	79.49(15.27)	78.31(17.83)	0.542	66.63(17.34)	62.54(13.46)	0.038
BUN(mmol/L)	5.36(1.93)	5.23(1.76)	0.305	5.55(1.52)	5.52(1.85)	0.868	5.22(2.31)	4.88(1.59)	0.183

Table 1. Continue

	Uighur								
	Total			Men			Women		
	EH	controls	P	EH	controls	P	EH	controls	P
Number (n)	181	292		103	210		78	82	
Age, mean (SD)	58.78(9.08)	58.30(9.36)	0.581	58.55(9.11)	58.51(9.43)	0.969	59.09(9.09)	59.33(8.98)	0.867
Diabetes (%)	26(14.4)	23(7.9)	0.024	13(12.6)	15(7.1)	0.139	12(15.4)	8(9.8)	0.282
Smoking (%)	26(14.36)	16(5.48)	0.001	26(25.2)	16(7.6)	<0.001	0	0	1
Drinking (%)	17(9.39)	12(4.11)	0.020	17(16.5)	11(5.2)	0.001	0	1(1.2)	0.328
BMI, mean (SD)	26.97(3.73)	26.54(4.69)	0.251	27.17(3.46)	26.69(3.96)	0.272	26.68(4.25)	26.17(4.33)	0.443
Glu(mmol/L)	5.89(2.56)	5.53(2.08)	0.101	5.82(2.60)	5.44(1.89)	0.156	5.99(2.51)	5.76(2.48)	0.561
TG(mmol/L)	1.84(1.16)	1.78(1.07)	0.629	1.71(1.00)	1.80(1.06)	0.484	2.00(1.33)	1.73(1.09)	0.179
TC(mmol/L)	4.31(1.34)	4.27(1.19)	0.697	4.22(0.98)	4.29(1.27)	0.635	4.44(1.31)	4.21(0.99)	0.235
HDL(mmol/L)	1.02(0.34)	1.03(0.36)	0.745	0.99(0.34)	1.02(0.36)	0.409	1.07(0.33)	1.06(0.36)	0.924
LDL(mmol/L)	2.77(0.99)	2.62(0.87)	0.115	2.74(0.93)	2.62(0.87)	0.291	2.80(1.07)	2.63(0.90)	0.300
UA(umol/L)	297.57(94.43)	293.25(94.41)	0.639	319.29(79.93)	312.23(94.76)	0.527	268.70(104.55)	244.73(76.66)	0.107
Cr(umol/L)	74.65(31.63)	72.33(30.79)	0.443	80.10(21.40)	78.08(33.35)	0.581	67.40(40.55)	57.69(15.34)	0.049
BUN(mmol/L)	5.51(2.02)	5.35(1.50)	0.327	5.75(1.91)	5.39(1.54)	0.086	5.19(2.12)	5.23(1.39)	0.913

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages.
BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DM, diabetes mellitus; Glu, glucose; TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein;
LDL, low density lipoprotein; UA, uric acid.
The P value of the continuous variables was calculated by the Independent t-test. The P value of the categorical variables was calculated by Fisher's exact test.

Distributions of CYP17A1 genotypes

As shown in Table 2, in the Han population, the distributions of the genotypes and alleles for each SNP were in good agreement with the predicted Hardy–Weinberg equilibrium values (data not shown). For the total, male, and female participants, the distribution of SNP1 (rs4919686), SNP2 (rs1004467), SNP3 (rs4919687) and SNP4 (rs10786712) genotypes did not show a significant difference between the EH patients and the control subjects (P>0.05) in the dominant, recessive, and additive models. For the total and female subjects, the distribution of the SNP5 (rs2486758) genotypes did not show a significant difference between the EH patients and the control subjects. For the male subjects, the distribution of SNP5 (rs2486758) showed a difference between the EH patients and the control subjects in a recessive model (TT+CT vs. CC; P=0.007).

As shown in Table 3, in the Uighur population, the distributions of the genotypes and alleles for each SNP were in good agreement with the predicted Hardy–Weinberg equilibrium values (data not shown). For the total, male, and female participants, the distribution of the SNP2 (rs1004467) genotypes did not show a significant difference between the EH and control subjects (P>0.05). For the total, the distribution of the SNP1 (rs4919686) genotypes, the dominant model (AC + CC vs AA), and the additive model (AA+AC vs CC) frequency showed significant difference between the EH and control subjects (P=0.020, P=0.025, P=0.007, respectively), and the dominant model and additive model were significantly lower in the subjects with EH than in the controls (26.5% vs. 36.7%, 21.8% vs. 33.8%). The distribution of the SNP3 (rs4919687) genotypes, the recessive model

(AG+GG vs AA), and the additive model (AA+GG vs. AG) showed a significant difference between the EH and control subjects (P<0.002, P=0.046, P=0.001, respectively), and the recessive model and additive model were significantly higher in the controls than in the EH subjects (88.2% vs 84.1%, 42.2% vs 26.7%). The distribution of the SNP4 (rs10786712) genotypes, the dominant model (CT + TT vs CC) and the allele frequency showed significant differences between the EH patients and the control subjects (P=0.004, P=0.001, P=0.001, respectively), and the dominant model and allele frequency were significantly higher in the EH subjects than in the controls (40.5% vs 26.0%, 62.7% vs 51.8%).

For men, the distribution of the SNP1(rs4919686) genotypes, dominant model (AC + CC vs AA), additive model (AA+AC vs CC) and allele frequency showed significant differences between the EH patients and the control subjects (P=0.004, P=0.002, P=0.001, P=0.014, respectively), and the dominant model, additive model, and allele frequency were significantly lower in the subjects with EH than in the controls (21.2% vs 38.7%, 17.2% vs 35.7%，12.6% vs 20.9%). The distribution of the SNP3 (rs4919687) genotypes, dominant model (AA + AG vs GG), recessive model (AG+GG vs AA), and additive model (AA+GG vs AG) showed significant differences between the EH and control subjects (P<0.001, P=0.044, P=0.026, P<0.001, respectively), and the dominant model, recessive model and additive model were significantly higher in the controls than in the EH subjects (59.2% vs 47.0%, 85.4% vs 75.0%, 44.7% vs 22.0%). The distribution of the SNP4 (rs10786712) genotypes, dominant model (CT + TT vs CC), recessive model (CT + CC vs TT), and allele frequency showed significant difference between the EH patients and the control subjects (P=0.002, P=0.001, P=0.013, P<0.001, respectively), and the dominant model, recessive model, and allele frequency were significantly higher in the EH subjects compared with the controls (44.0% vs 25.9%, 87% vs 74.6%，65.5% vs 50.2%).

For women, the distribution of the SNP5 (rs2486758) genotypes and recessive model (CT+TT vs CC) showed significant differences between the EH patients and control subjects (P=0.025, P=0.008, respectively), and the genotypes and recessive model frequency were significantly lower in the EH subjects than in the controls (54.0% vs 54.9%, 90.5% vs 100%).

Table 2. Genotype and Allele distributions in Han patients with EH and control participants

Variants		Total			Men			Women		
		EH n(%)	Control n(%)	P	EH n(%)	Control n(%)	P	EH n(%)	Control n(%)	P
Rs4919686 (SNP1)										
	AA	183(74.4)	203(78.4)		94(71.8)	111(78.2)		89(77.4)	92(78.6)	
Genotyping	AC	60(24.4)	53(20.5)	0.567	35(26.7)	29(20.4)	0.465	25(21.7)	24(20.5)	0.974
	CC	3(1.2)	3(1.2)		2(1.5)	2(1.4)		1(0.9)	1(0.9)	
Recessive model	CC	3(1.2)	3(1.2)	0.949	2(1.5)	2(1.4)	0.935	1(0.9)	1(0.9)	0.990
	AA+AC	243(98.8)	256(98.8)		129(98.5)	140(98.6)		114(99.0)	116(99.1)	
Dominant model	AA	183(74.4)	203(78.4)	0.291	37(28.2)	111(78.2)	0.221	89(77.4)	92(78.6)	0.819
	AC+CC	63(25.6)	56(21.6)		57(27.0)	31(21.8)		26(22.6)	25(21.4)	
Additive model	AC	60(24.4)	53(20.5)	0.290	35(26.7)	29(20.4)	0.220	25(21.7)	24(20.5)	0.819
	AA+CC	186(75.6)	206(79.5)		96(73.3)	113(79.6)		90(78.3)	93(79.5)	
Allele	A	426(86.6)	459(88.6)	0.329	223(85.1)	251(88.4)	0.260	203(88.3)	208(88.9)	0.832
	C	66(13.4)	59(11.4)		39(14.9)	33(11.6)		27(11.7)	26(11.1)	
Rs1004467 (SNP2)										
	CC	52(20.1)	46(15.9)		30(20.7)	24(15.3)		23(19.3)	22(16.5)	
Genotyping	CT	124(47.9)	158(54.7)	0.240	71(49.0)	88(56.1)	0.364	55(46.2)	70(52.6)	0.592
	TT	83(32.0)	85(29.4)		44(30.3)	45(28.7)		41(34.5)	41(30.8)	
Recessive model	CC	52(20.1)	46(15.9)	0.205	30(20.7)	24(15.3)	0.221	23(19.3)	22(16.5)	0.564
	CT+TT	207(79.9)	243(84.1)		115(79.3)	133(84.70		96(80.7)	111(83.5)	
Dominant model	TT	83(32.0)	85(29.4)	0.504	44(30.3)	45(28.7)	0.479	41(34.5)	41(30.8)	0.540
	CC+CT	176(68.0)	204(70.6)		101(69.7)	112(71.3)		78(65.5)	92(69.2)	
Additive model	CT	124(47.9)	158(54.7)	0.112	71(49.0)	88(56.1)	0.218	55(46.2)	70(52.6)	0.309
	CC+TT	135(52.1)	131(45.3)		74(51.0)	69(43.9)		64(53.8)	64(47.4)	
Allele	C	228(44.0)	250(43.3)	0.799	131(45.2)	136(43.3)	0.646	101(42.4)	114(42.9)	0.924
	T	290(56.0)	328(56.7)		159(54.8)	178(56.7)		137(57.6)	152(57.1)	

Rs4919687 (SNP3)										
	AA	9(3.4)	15(5.2)		5(3.5)	8(5.1)		4(3.4)	7(5.3)	
Genotyping	AG	90(34.4)	96(33.4)	0.590	49(34.3)	56(35.9)	0.724	41(34.5)	40(30.5)	0.641
	GG	163(62.2)	176(61.3)		89(62.2)	92(59.0)		74(62.2)	84(64.1)	
Recessive model	AA	9(3.4)	15(5.2)	0.305	5(3.5)	8(5.1)	0.489	4(3.4)	7(5.3)	0.445
	AG+GG	253(96.6)	272(94.8)		138(96.5)	148(94.9)		115(96.6)	124(94.7)	
Dominant model	GG	163(62.2)	176(61.3)	0.830	89(62.2)	92(59.0)	0.564	74(62.2)	84(64.1)	0.751
	AA+AG	99(37.8)	111(38.7)		54(37.8)	64(41.0)		45(37.8)	47(35.9)	
Additive model	AG	90(34.4)	96(33.4)	0.824	49(34.3)	56(35.9)	0.768	41(34.5)	40(30.5)	0.508
	AA+GG	172(65.6)	191(66.6)		94(65.7)	100(64.1)		78(65.5)	91(69.5)	
Allele	A	108(20.6)	126(22.0)	0.588	59(20.6)	72(23.1)	0.470	49(20.6)	54(20.6)	0.995
	G	416(79.4)	448(78.0)		227(79.4)	240(76.9)		189(79.4)	208(79.4)	
Rs10786712 (SNP4)										
	CC	50(20.2)	56(21.6)		29(21.8)	30(21.1)		21(18.3)	26(22.2)	
Genotyping	CT	126(50.8)	128(49.4)	0.915	62(46.6)	66(46.5)	0.985	64(55.7)	62(53.0)	0.754
	TT	72(29.0)	75(29.0)		42(31.6)	46(32.4)		30(26.1)	29(24.8)	
Recessive model	TT	72(29.0)	75(29.0)	0.985	42(31.6)	46(32.4)	0.885	30(26.1)	29(24.8)	0.820
	CC+CT	176(71.0)	184(71.0)		91(68.4)	96(67.6)		85(73.9)	88(75.2)	
Dominant model	CC	50(20.2)	56(21.6)	0.686	29(21.8)	30(21.1)	0.891	21(18.3)	26(22.2)	0.453
	CT+TT	198(79.8)	203(78.4)		104(78.2)	112(78.9)		94(81.7)	91(77.8)	
Additive model	CT	126(50.8)	128(49.4)	0.755	62(46.6)	66(46.5)	0.982	64(55.7)	62(53.0)	0.684
	CC+TT	122(49.2)	131(50.60		71(53.4)	76(53.5)		51(44.3)	55(47.0)	
Allele	C	226(45.6)	240(46.3)	0.806	120(45.1)	126(44.4)	0.860	106(46.1)	114(48.7)	0.570
	T	270(54.4)	278(53.7)		146(54.9)	158(55.6)		124(53.9)	120(51.3)	
Rs2486758 (SNP5)										
	CC	14(5.2)	6(2.1)		11(7.7)	2(1.3)		3(2.4)	4(3.1)	
Genotyping	CT	82(30.7)	103(36.4)	0.076	46(32.2)	57(36.5)	0.023	36(29.0)	46(36.2)	0.423
	TT	171(64.0)	174(61.5)		86(60.1)	97(62.2)		85(68.5)	77(60.6)	
Recessive model	CC	14(5.2)	6(2.1)	0.051	11(7.7)	2(1.3)	0.007	3(2.4)	4(3.1)	0.725
	CT+TT	253(94.8)	277(97.9)		132(92.3)	154(98.7)		121(97.6)	123(96.9)	
Dominant model	TT	171(64.0)	174(61.5)	0.535	86(60.1)	97(62.2)	0.718	85(68.5)	77(60.6)	0.190
	CC+CT	96(36.0)	109(38.5)		57(39.9)	59(37.8)		39(31.5)	50(39.4)	
Additive model	CT	82(30.7)	103(36.4)	0.158	46(32.2)	57(36.5)	0.427	36(29.0)	46(36.2)	0.225
	CC+TT	185(69.3)	180(63.6)		97(67.8)	99(63.5)		88(71.0)	81(63.8)	
Allele	C	110(20.6)	115(20.3)	0.908	68(23.8)	61(19.6)	0.210	42(16.9)	54(21.3)	0.218
	T	424(79.4)	451(79.7)		218(76.2)	251(80.4)		206(83.1)	200(78.7)	

EH, essential hypertension; N, number of participants; SNP, single-nucleotide polymorphism.

Logistic regression analyses

Table 4, Uighurshows, in the Uighur population for the total subjects and the men, the multivariable logistic regression analysis combining the genotypes with the following variables: the incidence of diabetes, smoking, and drinking as well as the BMI; after the multivariate adjustment, SNP1 (rs4919686) remained significantly associated with EH in the additive model (total: OR=0.559, 95%CI:0.356-0.879, P=0.012, men: OR=0.386, 95%CI: 0.211-0.706, P=0.002) and in the dominant model (total: OR=1.568, 95%CI: 0.324-0.934, P=0.027, men: OR=2.262, 95%CI: 1.285-3.980, P=0.005) (data not shown). After the multivariate adjustment, SNP3 (rs4919687) remained significantly associated with EH in the additive model (total: OR=0.520, 95%CI: 0.341-0.792, P=0.002, men: OR=0.371, 95%CI: 0.213-0.644, P<0.001) and in the recessive model (total: OR=1.840, 95%CI: 1.080-3.136, P=0.025, men: OR=1.954, 95%CI: 1.061-3.565, P=0.031) (data not shown).

The significant difference of SNP4 (rs10786712) (total: OR=1.968, 95%CI: 1.294-2.993, P=0.002, men: OR=2.189, 95%CI: 1.306-3.667, P=0.003) was retained after adjustment of the major confounding factors for EH in the dominant model.

Table 3. Genotype and Allele distributions in Uighur patients with EH and control participants

Variants		Total			Men			Women		
		EH n(%)	Control n(%)	P	EH n(%)	Control n(%)	P	EH n(%)	Control n(%)	P
Rs4919686 (SNP1)										
Genotyping	AA	125(73.5)	176(63.3)	0.020	78(78.8)	122(61.3)	0.004	47(66.2)	54(68.4)	0.626
	AC	37 (21.8)	94 (33.8)		17(17.2)	71(35.7)		20(28.2)	23(29.1)	
	CC	8 (4.7)	8 (2.9)		4(4.0)	6(3.0)		4(5.6)	2(2.5)	
Recessive	CC	8 (4.7)	8 (2.9)	0.312	4(4.0)	6(3.0)	0.643	4(5.6)	2(2.5)	0.333
model	AA+AC	162(95.3)	270(97.1)		95(96.0)	193(97.0)		67(94.4)	77(97.5)	
Dominant	AA	125(73.5)	176(63.3)	0.025	78(78.8)	122(61.3)	0.002	47(66.2)	54(68.4)	0.779
model	AC+CC	45(26.5)	102(36.7)		21(21.2)	77(38.7)		24(33.8)	25(31.6)	
Additive	AC	37 (21.8)	94 (33.8)	0.007	17(17.2)	71(35.7)	0.001	20(28.2)	23(29.1)	0.898
model	AA+CC	133(78.2)	184(66.2)		82(82.8)	128(64.3)		51(71.8)	56(70.9)	
Allele	A	287(84.4)	446(80.2)	0.114	173(87.4)	315(79.1)	0.014	114(80.3)	131(82.9)	0.557
	C	53(15.6)	110(19.8)		25(12.6)	83(20.9)		28(19.70	27(17.1)	
Rs1004467 (SNP2)										
Genotyping	CC	42(24.6)	72(25.2)	0.812	16(16.2)	37(17.9)	0.821	26(36.1)	35(43.8)	0.425
	CT	85(49.7)	148(51.7)		53(53.5)	114(55.1)		32(44.4)	35(43.8)	
	TT	44(25.7)	66(23.1)		30(30.3)	56(27.1)		14(19.4)	10(12.5)	
Recessive	CC	42(24.6)	72(25.2)	0.883	16(16.2)	37(17.9)	0.711	26(36.1)	35(43.8)	0.337
model	CT+TT	129(75.4)	214(74.8)		83(83.8)	170(82.1)		46(63.9)	45(56.3)	
Dominant	TT	44(25.7)	66(23.1)	0.521	30(30.3)	56(27.1)	0.554	14(19.4)	10(12.5)	0.241
model	CC+CT	127(74.3)	220(76.9)		69(69.7)	151(72.9)		58(80.6)	70(87.5)	
Additive	CT	85(49.7)	148(51.7)	0.673	53(53.5)	114(55.1)	0.801	32(44.4)	35(43.8)	0.931
model	CC+TT	86(50.3)	138(48.3)		46(46.5)	93(44.9)		40(55.6)	45(56.3)	
Allele	C	169(49.4)	292(51.0)	0.633	85(42.9)	188(45.4)	0.563	84(58.3)	105(65.6)	0.191
	T	173(50.6)	280(49.0)		113(57.1)	226(54.6)		60(41.7)	55(34.4)	
Rs4919687 (SNP3)										
Genotyping	AA	32(18.6)	34(11.8)	0.002	25(25.0)	30(14.6)	<0.001	7(9.7)	4(4.9)	0.518
	AG	46(26.7)	121(42.2)		22(22.0)	92(44.7)		24(33.3)	29(35.8)	
	GG	94(54.7)	132(46.0)		53(53.0)	84(40.8)		41(56.9)	48(59.3)	
Recessive	AA	32(18.6)	34(11.8)	0.046	25(25.0)	30(14.6)	0.026	7(9.7)	4(4.9)	0.253
model	AG+GG	140(81.4)	253(88.2)		75(75.0)	176(85.4)		65(90.3)	77(95.1)	
Dominant	GG	94(54.7)	132(46.0)	0.072	53(53.0)	84(40.8)	0.044	41(56.9)	48(59.3)	0.772
model	AA+AG	78(45.3)	155(54.0)		47(47.0)	122(59.2)		31(43.1)	33(40.7)	
Additive	AG	46(26.7)	121(42.2)	0.001	22(22.0)	92(44.7)	<0.001	24(33.3)	29(35.8)	0.749
model	AA+GG	126(73.3)	166(57.8)		78(78.0)	114(55.3)		48(66.7)	52(64.2)	
Allele	A	110(32.0)	189(32.9)	0.766	72(36.0)	152(36.9)	0.830	38(26.4)	37(22.8)	0.471
	G	234(68.0)	385(67.1)		128(64.0)	260(63.1)		106(73.6)	125(77.2)	
Rs10786712 (SNP4)										
Genotyping	CC	70(40.5)	73(26.0)	0.004	44(44.0)	52(25.9)	0.002	26(35.6)	21(26.3)	0.310
	CT	77(44.5)	145(51.6)		43(43.0)	98(48.8)		34(46.6)	47(58.8)	
	TT	26(15.0)	63(22.4)		13(13.0)	51(25.4)		13(17.8)	12(15.0)	
Recessive	TT	26(15.0)	63(22.4)	0.054	13(13.0)	51(25.4)	0.013	13(17.8)	12(15.0)	0.639
model	CC+CT	147(85.0)	218(77.6)		87(87.0)	150(74.6)		60(82.2)	68(85.0)	
Dominant	CC	70(40.5)	73(26.0)	0.001	44(44.0)	52(25.9)	0.001	26(35.6)	21(26.3)	0.210
model	CT+TT	103(59.5)	208(74.0)		56(56.0)	149(74.1)		47(64.4)	59(73.8)	
Additive	CT	77(44.5)	145(51.6)	0.142	43(43.0)	98(48.8)	0.346	34(46.6)	47(58.8)	0.132
model	CC+TT	96(55.5)	136(48.4)		57(57.0)	103(51.2)		39(53.4)	33(41.3)	
Allele	C	217(62.7)	291(51.8)	0.001	131(65.5)	202(50.2)	<0.001	86(58.9)	89(55.6)	0.563
	T	129(37.3)	271(42.2)		69(34.5)	200(49.8)		60(41.1)	71(44.4)	
Rs2486758 (SNP5)										
Genotyping	CC	11(6.6)	9(3.3)	0.151	5(4.9)	9(4.5)	0.289	6(9.5)	0	0.025
	CT	67(40.4)	100(36.6)		44(42.7)	68(33.8)		23(36.5)	32(45.1)	
	TT	88(53.0)	164(60.1)		54(52.4)	124(61.7)		34(54.0)	39(54.9)	
Recessive	CC	11(6.6)	9(3.3)	0.105	5(4.9)	9(4.5)	0.882	6(9.5)	0	0.008
model	CT+TT	155(93.4)	264(96.7)		98(95.1)	192(95.5)		57(90.5)	71(100)	
Dominant	TT	88(53.0)	164(60.1)	0.147	54(52.4)	124(61.7)	0.121	34(54.0)	39(54.9)	0.911
model	CC+CT	78(47.0)	109(39.9)		49(47.6)	77(38.3)		29(46.0)	32(45.1)	
Additive	CT	67(40.4)	100(36.6)	0.435	44(42.7)	68(33.8)	0.128	23(36.5)	32(45.1)	0.315
model	CC+TT	99(59.6)	173(63.4)		59(57.3)	133(66.2)		40(63.5)	39(54.9)	
Allele	C	89(26.8)	118(21.6)	0.079	54(26.2)	86(21.4)	0.181	35(27.8)	32(22.5)	0.323
	T	243(73.2)	428(78.4)		152(73.8)	316(78.6)		91(72.2)	110(77.5)	

EH, essential hypertension; N, number of participants; SNP, single-nucleotide polymorphism.

Table 4. Multiple logistic regression analysis for EH patients and control subjects

	Total			Men			Women		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
rs4919686									
Additive model (CC+CT vs TT)	0.559	0.356-0.879	0.012	0.386	0.211-0.706	0.002	0.998	0.487-2.044	0.995
Diabetes	1.538	0.808-2.929	0.190	1.606	0.691-3.737	0.271	1.430	0.527-3.877	0.482
Smoking	3.143	1.272-7.763	0.013	1.167	0.445-3.059	0.754	_	_	_
Drinking	0.979	0.313-3.063	0.971	0.856	0.263-2.792	0.797	_	_	_
BMI	1.013	0.694-1.065	0.615	1.016	0.951-1.086	0.630	1.021	0.946-1.102	0.592
rs4919687									
Additive model (CC+CT vs TT)	0.520	0.341-0.792	0.002	0.371	0.213-0.644	<0.001	0.939	0.478-1.844	0.854
Diabetes	1.457	0.769-2.761	0.249	1.591	0.703-3.599	0.265	1.268	0.460-3.499	0.646
Smoking	3.780	1.396-10.24	0.009	1.204	0.439-3.304	0.718	_	_	_
Drinking	0.688	0.202-2.346	0.550	0.739	0.209-2.605	0.638	-	_	-
BMI	1.020	0.970-1.073	0.437	1.029	0.963-1.099	0.396	1.024	0.948-1.106	0.551
rs10786712									
Dominant model (CC+CT vs TT)	1.968	1.294-2.993	0.002	2.189	1.306-3.667	0.003	1.454	0.717-2.949	0.299
Diabetes	1.366	0.709-2.630	0.351	1.438	0.613-3.370	0.404	1.284	0.470-3.509	0.626
Smoking	3.479	1.335-9.066	0.011	1.225	0470-3.195	0.678	_	_	_
Drinking	0.886	0.277-2.833	0.839	0.886	0.273-2.873	0.841	-	_	-
BMI	1.012	0.962-1.064	0.564	1.021	0.956-1.090	0.532	1.018	0.943-1.099	0.654

OR, odds ratios; 95%CI, 95% confidence intervals

For women, after the multivariate adjustment, SNP5 (rs2486758) did not remain significantly associated with EH in the recessive model (data not shown). Similarly, in the Han population, for men, the recessive model showed that for SNP5 (rs2486758), a significant difference was not retained after adjustment for the covariates.

LD analysis

In the Han population, all five of the SNPs are located in one haplotype block because the | D' | values were beyond 0.5, and all of the r^2 values were below 0.5; therefore, the five SNPs were used to construct the

haplotypes. In the Uighur population, because the | D' | for SNP1-SNP2, SNP2-SNP3, SNP2-SNP4, and SNP2-SNP5 were < 0.5, SNP2 could not be used to construct the haplotypes with another SNP; therefore, we constructed the haplotypes using SNP1, SNP3, SNP4, and SNP5.

Haplotype analyses

In the haplotype-based case-control analysis of the Han population, the haplotypes were established for males through the use of different combinations of the five SNPs (Table 5). The frequencies of the A–A–T, A–A–T, A–T–T–T and A–A–T–T haplotypes established by SNP1–SNP3–SNP4, SNP1–SNP3–SNP5, SNP1–SNP2–SNP4-SNP5, and SNP1–SNP3–SNP4–SNP5, respectively, were significantly higher for the control subjects than for the EH patients (P=0.049, P=0.030, P=0.044, and P=0.046, respectively). The distribution of the A–A and A–C–A haplotypes, established by SNP1–SNP3 and SNP1-SNP2–SNP3, respectively, showed a significant difference between the EH patients and the control subjects (P=0.041, P=0.032, respectively) as well. For the total and female subjects, the overall distribution of the haplotypes was not significantly different between the EH patients and the control subjects.

UighurIn the haplotype-based case-control analysis of the Uighur population, the haplotypes were established through the use of different combinations of the four SNPs (Table 6). For the total and males, the overall distribution of the haplotypes established by SNP1–SNP3, SNP1–SNP4, SNP1–SNP3–SNP5 and SNP1–SNP4–SNP5 were significantly different between the EH patients and the control subjects (for the total: P=0.013, P=0.008, P=0.032, and P=0.010, respectively; for the males：P<0.001, P=0.001, P=0.010, and P=0.002, respectively); the frequencies of the A-A, A-C, A-A-T and A-C-T haplotypes established by SNP1-SNP3，SNP1-SNP4，SNP1-SNP3-SNP5, and SNP1–SNP4–SNP5, respectively, were significantly higher for the EH patients than for the control subjects (for the total: P=0.032, P=0.002, P=0.039, P=0.039, respectively; for the males: P=0.012, P<0.001, P=0.033, P=0.009, respectively). The frequencies of the C-A-T, C-A-T, C-T-T and C-A-T-T haplotypes established by SNP1-SNP3-SNP4, SNP1-SNP3-SNP5, SNP1-SNP4-SNP5, and SNP1-SNP3-SNP4-SNP5, respectively, were lower for the EH patients than for the control subjects (for the total: P=0.015, P=0.009, P=0.021, P=0.005, respectively; for the males：P<0.001, P=0.001, P=0.003, P=0.001, respectively). For the males, the frequency of the A–A-C haplotype established by SNP1–SNP3-SNP4 and the A–A-C–T haplotype established by SNP1–SNP3–SNP4-SNP5 were significantly lower for the control subjects than for the EH patients (P=0.014 and P=0.006, respectively). For the females, the overall distribution of the haplotypes was not significantly different between the EH patients and the control subjects.

Table 5. Haplotype analysis in Han men patients with EH and in control subjects

Haplotypes					Haplotype Frequencies		X^2	P	OR	95%CI
SNP1	SNP2	SNP3	SNP4	SNP5	EH	Control				
A		A			0.077	0.128	4.156	0.041	0.562	0.321-0.984
A	C	A			0.009	0.035	4.616	0.032	0.244	0.061-0.980
A		A	T		0.071	0.118	3.876	0.049	0.563	0.316-1.103
A		A		T	0.067	0.120	4.686	0.030	0.525	0.290-0.948
A	T		T	T	0.071	0.121	4.042	0.044	0.555	0.311-0.991
A		A	T	T	0.070	0.119	3.991	0.046	0.554	0.309-0.995

EH, essential hypertension; haplotype with frequencies > 0.03 were estimated using SHEsis software; SNP, single-nucleotide polymorphism; OR, odds ratio.

Table 6. Haplotype analysis in patients with EH and in control subjects (Uygur)

	1	2	3	4	Overall P value			Frequency in total			Frequency in man			Frequency in woman		
					Total	Man	Woman	EH	Control	P value	EH	Control	P value	EH	Control	P value
	SNP1	SNP3			0.013	< 0.001	0.268									
H1	A	A						0.207	0.150	0.032	0.277	0.186	0.012	0.108	0.069	0.127
H2	C	A						0.117	0.179	0.014	0.081	0.187	<0.001	0.169	0.259	0.833
	SNP1		SNP4		0.008	0.001	0.570									
H1	A		C					0.625	0.518	0.002	0.660	0.505	<0.001	0.570	0.557	0.814
H3	C		T					0.155	0.198	0.103	0.124	0.216	0.014	0.204	0.171	0.459
		SNP3	SNP4		0.008	<0.001	0.154									
H1		A	C					0.125	0.083	0.044	0.199	0.105	0.002	0.017	0.026	_
H2		A	T					0.199	0.246	0.105	0.165	0.268	0.006	0.251	0.195	0.262
H4		G	T					0.177	0.241	0.024	0.184	0.232	0.180	0.169	0.254	0.067
	SNP1	SNP3	SNP4		0.002	<0.001	0.053									
H2	C	A	T					0.118	0.179	0.015	0.081	0.187	<0.001	0.169	0.159	0.860
H3	A	A	C					0.122	0.083	0.065	0.194	0.106	0.003	0.017	0.027	_
	SNP1	SNP3		SNP5	0.032	0.010	0.378									
H1	A	A		T				0.165	0.117	0.039	0.205	0.137	0.033	0.101	0.066	0.265
H2	C	A		T				0.107	0.176	0.009	0.081	0.184	0.001	0.151	0.151	0.880
	SNP1		SNP4	SNP5	0.010	0.002	0.771									
H1	A		C	T				0.372	0.307	0.039		0.412	0.304	0.009	0.296	0.319
H2	C		T	T				0.134	0.198	0.021		0.109	0.207	0.003	0.187	0.167
	SNP1	SNP3	SNP4	SNP5	0.003	0.003	0.093									
H1	A	G	T	T				0.138	0.220	0.005		0.138	0.207	0.046	0.135	0.251
H2	C	A	T	T				0.103	0.175	0.005		0.082	0.183	0.001	0.149	0.151
H3	A	A	C	T				0.084	0.055	0.099		0.133	0.066	0.007	0.009	0.028

EH, essential hypertension; haplotype with frequencies >0.03 were estimated using SHEsis software; P value was calculated by permutation test using the bootstrap method; SNP, single-nucleotide polymorphism.

DISCUSSION

In our study, we found that variations in the CYP17A1 gene were associated with EH in a Uighur population of China.

Numerous CYP subfamilies, such as CYP2C9 (EET synthesis) [30], CYP4A11 (20-HETE synthesis) [31], CYP8A1 (prostacyclin synthesis) [32], and CYP11B2 (aldosterone synthesis) [33], have been shown to be associated with EH. The P450c17 proteins have two types of enzyme activity, and P450c17 is an important enzyme that catalyzes the formation of all endogenous androgens. Therefore, CYP17A1 genetic mutations could cause the loss of the enzyme activity of P450c17 and potentially reduce androgen biosynthesis. Androgens serve as precursors to estrogens; normal estrogen signaling is dependent on CYP17A1 as well. The mechanism by which the CYP17A1 gene leads to hypertension is unclear. Recently, animal experiments and clinical observations have demonstrated that the occurrence of hypertension is

related to the levels of sex hormones in the body [34]. A clinical study [35] showed that testosterone levels play an important role in the progression of hypertension in elderly men, whereas lower testosterone levels promote hypertension. The incidence of hypertension among premenopausal women was significantly lower than that among men [36]. Therefore, estrogen likely plays a protective role in the cardiovascular system.

We found that polymorphisms of CYP17A1 were associated with EH in the Uighur population. In total and in the men, for SNP1 (rs4919686), the frequency of AC genotypes is higher in the control subjects than in the EH subjects, and there were significant differences in the genotypes, dominant model, and additive model, after multivariate adjustment of the confounding factors for EH. The significant difference was retained, which indicated that the AC genotypes might be protective against EH; the frequency of the A allele is higher in the EH patients than in the control subjects, which indicated that the A allele is a risk factor for EH. For SNP3 (rs4919686), the frequency of the AG genotypes is higher in the control subjects than in the EH subjects, and there were significant differences in the genotypes, recessive model, and additive model; the significant difference was retained after the multivariate adjustment of the confounding factors for EH, which indicated that the AG genotypes might be protective against EH. For SNP4 (rs10786712), the frequency of the TT genotypes and the T allele are higher in the control subjects than in the EH subjects, and there were significant differences in the genotypes, dominant model, and allele frequency; after the multivariate adjustment of the confounding factors for EH, the significant difference was retained, which indicated that the TT genotypes and T allele might be protective against EH. In addition, based on such findings, we hypothesized that a haplotype analysis would be useful for the assessment of the associations between haplotypes and EH. For the total and the men, we succeeded identifying four susceptible haplotypes (A-A of SNP1-SNP3, A-C of SNP1-SNP4, A-A-T of SNP1-SNP3-SNP5, and A-C-T of SNP1-SNP4-SNP5), and these haplotypic analysis results are consistent with the genotypic analysis results for SNP1 (rs4919686), which showed that the A allele confers risk. Additionally, we identified four protective haplotypes (C-A-T of SNP1-SNP3-SNP4, C-A-T of SNP1-SNP3-SNP5, C-T-T of SNP1-SNP4-SNP5, and C-A-T-T of SNP1-SNP3-SNP4-SNP5), and these haplotypic analysis results are consistent with the genotypic analysis results of SNP4 (rs10786712), which showed that the T allele is protective. For women, the overall distribution of this haplotype was not significantly different between the EH patients and the control subjects (all P>0.05).

In the Han population, for men, the distribution of the SNP5 (rs2486758) recessive model (TT+CT *vs.* CC) showed a difference between EH and the control subjects (P=0.007); however, in the recessive model of SNP5 (rs2486758), a significant difference was not retained after adjustment for the covariates (date not shown). In addition, based on these findings, we hypothesized that haplotype analysis would be useful for the assessment of associations between haplotypes and EH. In men, we identified six protective haplotypes (A–A of SNP1–SNP3, A–C–A of SNP1–SNP2–SNP3, A–A–T of SNP1–SNP3-SNP4, A–A–T of SNP1–SNP3-SNP5, A–T–T–T of SNP1–SNP2–SNP4–SNP5, and A–A–T–T of SNP1–SNP3–SNP4–SNP5), which indicated that the A allele of SNP1 (rs4919686), the A allele of SNP3 (rs4919687), the T allele of SNP4 (rs10786712), and the T allele of SNP5 (rs2486758) could be protective genetic markers of EH. Four types of alleles could decrease the risk of hypertension.

This study is the first to investigate the differences between human CYP17A1 and EH in the Chinese population and is the first haplotype-based case–control study of the correlations of CYP17A1 with EH. In the Uighur population, for the total and the men, the A allele of rs4919686 could be a susceptible genetic marker, the AC genotype could be a protective genetic marker of EH, and the AG genotype of rs4919687 and the TT genotype of rs10786712 might be protective against EH. This study was limited by the relatively small sample size, and a large number of clinical samples and investigation of other SNPs of CYP17A1 would be required for future studies. Additional studies are necessary to isolate the functional mutations that associate the polymorphism of the CYP17A1 gene with EH.

Limitations of this Study

This study was limited by the relatively small sample size, which might have led to weak statistical significance and wide CIs in the estimation of the OR.

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