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=0.010, 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...
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 r²≥ 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 significantly 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 |                | Han men |                | Han women |                |
|---------------------|----------|----------------|---------|----------------|-----------|----------------|
|                     | EH controls | P | EH controls | P | EH controls | P |
| Number (n)          | 270 | 288 | 0.264 | 145 | 157 | 0.779 | 125 | 131 | 0.103 |
| 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(10.03) | 0.264 | 26.94(11.08) | 26.19(11.19) | 0.540 | 27.14(7.71) | 26.83(8.2) | 0.103 |
| 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) | 0.069 | 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) | 0.065 | 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

|               | Total            | Uighur          | Women          |
|---------------|------------------|-----------------|----------------|
|               | EH controls P    | EH men controls P | EH women controls P |
| Number (n)    | 181             | 103             | 78             |
| Age, mean (SD)| 58.78(9.08)     | 58.51(9.43)     | 59.09(9.09)    |
| Diabetes (%)  | 26(14.4)        | 15(7.1)         | 12(15.4)       |
| Smoking (%)   | 26(14.36)       | 16(7.6)         | <0.001         |
| Drinking (%)  | 17(9.39)        | 11(5.2)         | 0              |
| BMI, mean (SD)| 26.97(3.73)     | 26.54(3.46)     | 26.68(4.25)    |
| Glu(mmol/L)   | 5.89(2.56)      | 5.44(1.89)      | 5.99(2.51)     |
| TG(mmol/L)    | 1.84(1.16)      | 1.80(1.06)      | 2.00(1.33)     |
| TC(mmol/L)    | 4.31(1.34)      | 4.29(1.27)      | 4.44(1.31)     |
| HDL(mmol/L)   | 1.02(0.34)      | 0.99(0.34)      | 1.07(0.33)     |
| LDL(mmol/L)   | 2.77(0.99)      | 2.74(0.93)      | 2.80(1.07)     |
| UA(umol/L)    | 297.57(94.43)   | 319.29(79.93)   | 268.70(104.55) |
| Cr(umol/L)    | 74.65(31.63)    | 80.10(21.40)    | 76.40(40.55)   |
| BUN(mmol/L)   | 5.51(2.02)      | 5.75(1.91)      | 5.19(2.12)     |

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=0.002, P=0.001, respectively), and the dominant 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 frequency were significantly 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

| Genotyping | Allele | Men | Women |
|------------|-------|-----|-------|
| **Rs4919686 (SNP1)** | | | |
| AA | 183(74.4) | 203(78.4) | 89(77.4) | 92(78.6) |
| AC | 60(24.4) | 53(20.5) | 25(21.7) | 24(20.5) |
| CC | 3(1.2) | 3(1.2) | 1(0.9) | 1(0.9) |
| **Recessive model** | | | | |
| AA+AC | 243(98.8) | 256(98.8) | 114(99.0) | 116(99.1) |
| **Dominant model** | | | | |
| AA | 183(74.4) | 203(78.4) | 89(77.4) | 92(78.6) |
| AC+CC | 63(25.6) | 56(21.6) | 26(22.6) | 25(21.4) |
| **Additive model** | | | | |
| AC | 60(24.4) | 53(20.5) | 25(21.7) | 24(20.5) |
| AA+CC | 186(75.6) | 206(79.5) | 90(78.3) | 93(79.5) |
| **Allele** | | | | |
| A | 426(86.6) | 459(88.6) | 203(88.3) | 208(88.9) |
| C | 66(13.4) | 59(11.4) | 27(11.7) | 26(11.1) |

| Genotyping | Allele | Men | Women |
|------------|-------|-----|-------|
| **Rs1004467 (SNP2)** | | | |
| CC | 52(20.1) | 46(15.9) | 23(19.3) | 22(16.5) |
| CT | 124(47.9) | 158(54.7) | 55(46.2) | 70(52.6) |
| TT | 83(32.0) | 85(29.4) | 41(34.5) | 41(30.8) |
| **Recessive model** | | | | |
| CC+CT | 207(79.9) | 243(84.1) | 93(80.7) | 111(83.5) |
| **Dominant model** | | | | |
| TT | 83(32.0) | 85(29.4) | 41(34.5) | 41(30.8) |
| CC+TT | 176(68.0) | 204(70.6) | 78(65.5) | 92(69.2) |
| **Additive model** | | | | |
| CT | 124(47.9) | 158(54.7) | 55(46.2) | 70(52.6) |
| CC+TT | 153(52.1) | 131(45.3) | 64(53.8) | 64(47.4) |
| **Allele** | | | | |
| C | 228(44.0) | 250(43.3) | 101(42.4) | 114(42.9) |
| T | 290(56.0) | 328(56.7) | 137(57.6) | 152(57.1) |
Logistic regression analyses

Table 4. Uighur shows, 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 (rs4919687) 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: 1.240-1.983, P=0.001) and the recessive model (total: OR=0.792, 95%CI: 0.613-1.012, P=0.051). The significant difference of SNP4 (rs10786712) (total: OR=1.954, 95%CI: 1.061-3.565, P=0.031) was retained after adjustment of the major confounding factors for EH in the dominant model.

C.F. Dai et al.  
CYP17A1 genetic polymorphism and hypertension

| Rs4919687 (SNP3) |   |   |   |   |
|-------------------|---|---|---|---|
| Genotyping       |   |   |   |   |
| AG                | 9(3.4) | 15(5.2) | 5(3.5) | 8(5.1) |
| GG                | 163(62.2) | 176(61.3) | 89(62.2) | 92(59.0) |
| Recessive model   |   |   |   |   |
| AA                | 9(3.4) | 15(5.2) | 5(3.5) | 8(5.1) |
| AG+GG             | 253(96.6) | 272(94.8) | 138(96.5) | 148(94.9) |
| Dominant model    |   |   |   |   |
| AA+AG             | 99(37.8) | 111(38.7) | 54(37.8) | 64(41.0) |
| Additive model    |   |   |   |   |
| AG                | 90(34.4) | 96(33.4) | 49(34.3) | 56(35.9) |
| GG                | 172(65.6) | 191(66.6) | 94(65.7) | 100(64.1) |
| Allele            |   |   |   |   |
| A                 | 108(26.2) | 126(22.0) | 59(20.6) | 72(23.1) |
| G                 | 416(79.4) | 448(78.0) | 227(79.4) | 240(76.9) |

Rs10786712 (SNP4)

| Genotyping       |   |   |   |   |
| CT                | 126(50.8) | 128(49.4) | 62(46.6) | 66(46.5) |
| TT                | 2(50.0) | 2(50.0) | 2(100) | 2(100) |
| Recessive model   |   |   |   |   |
| CC+CT             | 176(71.0) | 184(71.0) | 91(68.4) | 96(67.6) |
| Dominant model    |   |   |   |   |
| CC+CT             | 198(79.8) | 203(78.4) | 104(78.2) | 112(78.9) |
| Additive model    |   |   |   |   |
| CT                | 126(50.8) | 128(49.4) | 62(46.6) | 66(46.5) |
| CC+CT             | 122(49.2) | 131(50.6) | 71(53.4) | 76(53.5) |
| Allele            |   |   |   |   |
| C                 | 226(45.6) | 240(46.3) | 120(45.1) | 124(46.4) |
| T                 | 270(54.4) | 278(53.7) | 146(54.9) | 158(55.6) |

Rs2486758 (SNP5)

| Genotyping       |   |   |   |   |
| CT                | 82(30.7) | 103(36.4) | 46(32.2) | 57(36.5) |
| TT                | 171(64.0) | 174(61.5) | 86(60.1) | 97(62.2) |
| Recessive model   |   |   |   |   |
| CC+CT             | 332(94.8) | 330(94.8) | 180(93.2) | 182(92.3) |
| Dominant model    |   |   |   |   |
| CC+CT             | 253(94.8) | 277(97.9) | 132(92.3) | 154(98.7) |
| Additive model    |   |   |   |   |
| CT                | 82(30.7) | 103(36.4) | 46(32.2) | 57(36.5) |
| CC+CT             | 185(69.3) | 180(63.6) | 97(67.8) | 99(63.5) |
| Allele            |   |   |   |   |
| C                 | 110(20.6) | 115(20.3) | 68(23.8) | 69(21.9) |
| T                 | 424(79.4) | 451(79.7) | 218(76.2) | 251(78.4) |

EH, essential hypertension; N, number of participants; SNP, single-nucleotide polymorphism.
Table 3. Genotype and Allele distributions in Uighur patients with EH and control participants

| Variant | EH n(%) | Control n(%) | P      | EH n(%) | Control n(%) | P  | Women | Control n(%) | P     |
|---------|---------|--------------|--------|---------|--------------|----|--------|--------------|-------|
| Rs4919686 (SNP1) |         |              |        |         |              |    |        |              |       |
| Genotyping | A 125(73.5) | 176(63.3) | 0.020 | 78(78.8) | 122(61.3) | 0.004 | 47(66.2) | 54(68.4) | 0.626 |
|           | C <0.001 |        |        | <0.001 |          |      | 0.004  |            |       |
| Recessive | A 8(4.7)  | 8(2.9)      | 0.312 | 4(4.0)  | 6(3.0)     | 0.643 | 4(5.6)  | 2(2.5)   | 0.333 |
| Additive  | A 125(73.5) | 176(63.3) | 0.025 | 78(78.8) | 122(61.3) | 0.002 | 47(66.2) | 54(68.4) | 0.779 |
| 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 |
| Rs1004467 (SNP2) |         |              |        |         |              |    |        |              |       |
| Genotyping | C 42(24.6)  | 72(25.2)    | 0.812 | 16(16.2)| 37(17.9)   | 0.821 | 26(36.1)| 35(43.8)| 0.425 |
|           | A 85(49.7) | 148(51.7)   | 0.002 | 53(53.5)| 114(55.1)  | 1.000 | 32(44.4)| 35(43.8)| 0.235 |
| Recessive | C 44(25.7) | 66(23.1)    | 0.883 | 16(16.2)| 37(17.9)   | 0.711 | 26(36.1)| 35(43.8)| 0.337 |
| Additive  | C 129(75.4) | 214(74.8)  | 0.001 | 83(83.8)| 170(82.1)  | 1.000 | 46(63.9)| 45(56.3)| 0.241 |
| Allele    | C 169(49.4) | 292(51.0)  | 0.633 | 85(42.9)| 188(45.4)  | 0.563 | 84(58.3)| 105(66.6)| 0.191 |
| Rs4919687 (SNP3) |         |              |        |         |              |    |        |              |       |
| Genotyping | A 32(18.6) | 34(11.8)    | 0.002 | 25(25.0)| 30(14.6)   | <0.001| 7(9.7) | 14(4.9) | 0.518 |
|           | G 46(26.7) | 121(42.2)   |        | 22(22.0)| 94(44.7)   | 0.008 | 32(44.4)| 29(35.8)| 0.175 |
| Recessive | A 32(18.6) | 34(11.8)    | 0.046 | 25(25.0)| 30(14.6)   | 0.026 | 7(9.7) | 4(4.9) | 0.253 |
| Additive  | G 140(81.4)| 253(88.2)   |        | 75(75.0)| 176(85.4)  | 0.001 | 65(90.3)| 77(95.1)| 0.772 |
| Allele    | A 78(45.3) | 155(54.0)   |        | 47(47.0)| 122(59.2)  | 0.001 | 31(41.3)| 33(40.7)| 0.101 |
| Rs10786712 (SNP4) |         |              |        |         |              |    |        |              |       |
| Genotyping | C 70(40.5) | 73(26.0)    | 0.004 | 44(44.0)| 52(25.9)   | 0.002 | 26(35.6)| 21(26.3)| 0.310 |
|           | A 41(22.8) | 116(41.3)   | 0.000 | 22(22.0)| 69(36.8)   | 0.001 | 12(15.6)| 15(17.5)| 0.639 |
| Recessive | C 26(15.0) | 63(22.4)    | 0.054 | 13(13.0)| 51(25.4)   | 0.001 | 13(17.8)| 12(15.0)| 0.639 |
| Additive  | C 147(85.0)| 218(77.6)   |        | 87(87.0)| 150(74.6)  | 0.001 | 60(82.6)| 68(85.0)| 0.772 |
| Allele    | C 129(37.3)| 271(42.2)   |        | 69(43.5)| 200(49.8)| <0.001 | 86(58.9)| 98(65.6)| 0.563 |
| Rs2486758 (SNP5) |         |              |        |         |              |    |        |              |       |
| Genotyping | C 11(6.6)  | 9(3.3)      | 0.151 | 5(4.9)  | 9(4.5)     | 0.289 | 6(9.5) | 0     | 0.025 |
|           | T 67(40.4) | 100(36.6)   |        | 44(42.7)| 68(33.8)| <0.001 | 23(36.5)| 32(45.1)| 0.004 |
| Recessive | C 88(53.0) | 164(60.1)   | 0.105 | 5(4.9)  | 9(4.5)     | 0.882 | 6(9.5) | 0     | 0.008 |
| Additive  | C 155(93.4)| 264(96.7)   |        | 98(95.1)| 192(95.5)| 0.001 | 57(90.5)| 7(100) | 0.911 |
| Allele    | C <0.001 |        |        | <0.001 |          |      | 0.004  |            |       |

EH, essential hypertension; N, number of participants; SNP, single-nucleotide polymorphism.
Table 4. Multiple logistic regression analysis for EH patients and control subjects

| SNP         | 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 | 0.694-1.605 | 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 | 0.439-3.04 | 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 | 0.470-3.195 | 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

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 r² values were below 0.5; therefore, the five SNPs were used to construct the haplotype.

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.
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.

In 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–SNP3–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)

| SNP1 | SNP3 | SNP4 | SNP5 |
|------|------|------|------|
| H1   | A    | A    |      |
| H2   | C    | A    |      |
| H3   | C    | T    |      |
| H4   | G    | T    |      |
| H5   | A    | C    | T    |
| H6   | A    | C    | T    |
| H7   | A    | G    | T    |
| H8   | C    | A    | T    |
| H9   | A    | C    | C    |

Overall P value: 0.013, <0.001, 0.268

| Overall P value | Frequency in total | Frequency in man | Frequency in woman |
|-----------------|--------------------|------------------|--------------------|
| Total           | EH Control P value | EH Control P value | EH Control P value |
| SNPs            |                    |                  |                    |
| SNP1 SNP3 SNP4 |                    |                  |                    |
| 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 SNP3 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 |
| H2 C T          | 0.155 0.198 0.103 0.124 0.216 0.014 | 0.204 0.171 0.459 |
| SNP3 SNP4 SNP5 | 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 SNP4 | 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 SNP3 SNP5 | 0.100 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 | 0.003 0.003 0.093 |
| H1 C 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 C      | 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 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. 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 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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