MEDICAL SCIENCE MONITOR

MOLECULAR BIOLOGY

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 2488-2499
DOI: 10.12659/MSM.902109

Received: 2016.10.26
Accepted: 2016.11.14
Published: 2017.05.24

Association of CYP17A1 Genetic Polymorphisms and Susceptibility to Essential Hypertension in the Southwest Han Chinese Population

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACEFG 1 Qian Li
BCD 1 Tangxin Gao
BCD 1 Yuncang Yuan
BCG 2 Yanrui Wu
CE 1 Qionglin Huang
BC 1 Fei Xie
AD 1 Pengzhan Ran
C 1 Lijuan Sun
AEFG 1 Chunjie Xiao

1 School of Medicine, Yunnan University, Kunming, Yunnan, P.R. China
2 Department of Cell Biology and Genetics, Kunming Medical University, Kunming, Yunnan, P.R. China

Corresponding Author: Chunjie Xiao, e-mail: chjxiao@ynu.edu.cn
Source of support: (No. U0932603) the National Nature Science Foundation of China; (from Qian Li) "The Academic Young Scholar of Distinction for Doctoral Post Graduate in Yunnan Province"; (No. 2013FZ053, 2013Y288, 2014FB005) the Basic Research Programs of Science Foundation of Yunnan Province

Background: The *CYP17A1* gene encodes for cytochrome P450 enzyme CYP17A1, which is involved with the steroidogenic pathway including mineralocorticoids. The *CYP17A1* polymorphisms might affect enzyme activity, then leading to a state of mineralocorticoid 11-deoxycorticosterone excess characterized by hypertension, suppressed plasma renin activity, and low aldosterone concentrations. The aim of this study was to investigate the contribution of *CYP17A1* polymorphisms in inducing the susceptibility to essential hypertension among the Southwest Han Chinese population.

Material/Methods: Eight single nucleotide polymorphisms of *CYP17A1* were genotyped in a case-control study for samples by polymerase chain reaction-restriction fragment length polymorphism analysis.

Results: The polymorphisms rs11191548 and rs4919687 were significantly associated with hypertension risk, which was confirmed by systolic and diastolic blood pressure distribution analyses between different genotype groups, and these two polymorphisms were found in linkage disequilibrium. The rs4919687 polymorphism was estimated to cause the destruction of exonic splicing silencer (ESR and Motif 3) sites and to transform the transcription factor AREB6 binding site, respectively, in the bioinformatics analyses. The haplotypes rs4919686A-rs3740397G -rs4919687C-rs743572C-rs11191548C and rs4919686A-rs3740397G-rs4919687T-rs743572C- rs11191548T were found to be susceptible to essential hypertension.

Conclusions: Our findings suggest that the *CYP17A1* polymorphisms could be a genetic risk factor for essential hypertension among the Yunnan Han Chinese population, which would have implications for the treatment of this complex disorder.

MeSH Keywords: Genetic Association Studies • Genetics, Population • Hypertension • Polymorphism, Single Nucleotide

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/902109

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Essential hypertension (EH) has become a major public-health concern in the world, and it is supposed to be associated with the increased risk of cardiovascular and kidney disease [1–3]. In China, about 153 million (18%) Chinese adults were hypertensive in 2002 [4]. It is estimated that 29.2% (range, 28.8–29.7%) of the world population will have hypertension by 2025, increasing by about 60% [2]. EH is considered to be a multifactorial inherited disease impacted with the interactions of genetic (polygenic predisposition) and environmental (obesity, alcohol excess, smoking, dietary sodium intake) factors [5]. Nearly 30–50% of the blood pressure (BP) variation among the population can be attributed to the genetic risks [6]. Over the last decade, scientists have found many gene variants associated with EH [7,8].

The *CYP17A1* gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins were supposed to be involved with endogenous metabolites, such as aldosterone, and sex hormones, epoxyeicosatrienoic acids, hydroxyeicosatetraenoic acids, and prostacyclin in the maintenance of cardiovascular health [9]. Recently, genome-wide association studies (GWAS) have screened the polymorphisms in this gene associated with hypertension [10–13]. Several studies have examined the association of the *CYP17A1* polymorphisms (rs11191548, rs1004467, rs3824755, rs2486758, rs12413409) with hypertension risk among the populations of Sweden [14], Korea [15,16], Japan [13,17], Europe [12,18,19], Beijing [20], Shanghai [20,21], Shandong [22], and Fujian [23] province, as well as in the population of Chinese children [24,25], with inconsistent results. There are limited data on the *CYP17A1* genetic determinants of EH for the patients among the Han Chinese population in Yunnan province.

The *CYP17A1* gene is mapped in the chromosome 10q24.32, which spans 8673 bp, including eight exons and seven introns, and is expressed in both adrenals and gonads [26]. This gene produces the P450c17 protein, a key enzyme in the steroidogenic pathway that generates 17α-hydroxylase and 17,20-lyase [26,27]. Indeed, polymorphisms in this gene would cause the deficiency of 17α-hydroxylase (17-OHD) [28–32]. A deficiency in CYP17A1 enzyme activity would induce the congenital disorders, characterized with sexual infantilism, hypertension, and abnormal levels of the renin–angiotensin–aldosterone system (RAAS) components [33]. On account of the accumulation of 11-deoxycorticosterone and corticosterone, almost all patients with 17OHD experienced hypertension or hypokalemia [34], strongly suggesting that the deficiency in CYP17A1 enzyme activity could have impacts on the pathogenesis of hypertension.

In this case-control study, we aimed to assess the association between the *CYP17A1* polymorphisms and essential hypertension among the Han Chinese population in Yunnan province, attempting to provide a new insight into the biology of BP regulation and the impact on public health and clinical care.

Material and Methods

Study population

Each subject of the Southwestern Han Chinese population was a resident of Yunnan province. The samples, which consisted of 510 patients with EH, were enrolled in the hypertension clinic of the Third People's Hospital and Kunming Yan'an Hospital. The group of patients met the 1999 World Health Organization criteria (WHO/ISH criteria) for hypertension (defined as an SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg) [35]. Patients diagnosed with secondary hypertension, cerebrovascular accident, myocardial infarction, or other serious diseases were ruled out. As a control population, 510 subjects unrelated to the patients were randomly selected from healthy examined people in the Third People's Hospital and Kunming Yan'an Hospital. The control population were without any history of chronic diseases and were based on comparable gender- and age-matched hypertensive counterparts. These individuals had normal BP (defined as SBP <120 mm Hg and DBP <80 mm Hg) and no history of receiving antihypertensive medication. The whole group provided written informed consent to participate in the study, and the consent authorization for publication was on file. This study was approved by the ethics committee of the School of Medicine of Yunnan University, and was performed in accordance with the principles of Declaration of Helsinki.

Clinical measurements

For the sample collection, questionnaires were used to collect information involved with the history of hypertension, medications, and anthropometric parameters of patients. After at least 30 minutes of rest, measurements were performed by using standard mercury sphygmomanometers on the right arm of subjects in the sitting position. SBP was determined by the onset of the "tapping" Korotkoff sound and DBP by the fourth Korotkoff sound. The BP measurements were performed at 5-minute intervals 3 times, and the average value was used for analysis.

Selection of single nucleotide polymorphisms (SNPs)

The common SNPs (minor allele frequency [MAF] >1%) of *CYP17A1* were obtained from the Han Chinese data set of the International HapMap Consortium (*http://www.hapmap.org/index.html.ja*). The tag SNPs were screened under the standard of r^2 ≥0.8 by using Haploview4.1 software (*http://www.broad.mit.*

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. The tag SNPs of *CYP17A1* gene.

Tag SNP	Captured SNP
rs743572	rs10786712 rs6163 rs6162 rs3781287 rs743572
rs1004467	rs17115100 rs3824755 rs1004467
rs4919687	rs10883783 rs4919687
rs755443	rs755443
rs3740397	rs3740397
rs4919686	rs4919686
rs762563	rs762563

The r^2 of each Tag SNP with its captured SNPs were more than 0.8.

edu/mpg/haploview). Seven tag SNPs (rs743572, rs1004467, rs4919687, rs755443, rs3740397, rs4919686, rs762563) and another well-studied polymorphism (rs11191548) were selected (Table 1) for this study. The *CYP17A1* gene structure and relative location of these eight SNPs are shown in Figure 1.

Genotyping

Genomic deoxyribonucleic acid (DNA) samples were extracted from the peripheral blood leukocytes of the subjects by the phenol-chloroform method and then stored at -70°C. The genotypes of eight SNPs were examined by the method of polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) analysis among all 1020 subjects. The information about the primer sequences and the restriction enzymes applied for the genotyping is shown in Table 2. The genotyping call rates for all eight SNPs were 98.9% (1009/1020). To guarantee the accuracy of genotyping, 50 randomly selected samples were repeated for each SNP, and 100% concordance was observed between the results of the two tests. In addition, 50 samples were randomly selected for direct sequencing, and 100% concordance was observed between these two genotyping methods.

Statistical analysis

The quantitative variables and categorical variables were expressed as the mean ± standard deviation and percentages, respectively. The Hardy-Weinberg equilibrium analyses for each SNP were calculated by using the chi-square test (χ^2 test). The rs1004467 and rs762563 were ruled out for the further analyses, because they were not in the Hardy-Weinberg equilibrium P<0.001. The rs755443 was also ruled out for the further analyses, because the frequency of AA genotype for this polymorphism was close to be 0, leading to the inaccurate results. The analysis of covariance (ANCOVA) was used to compare the

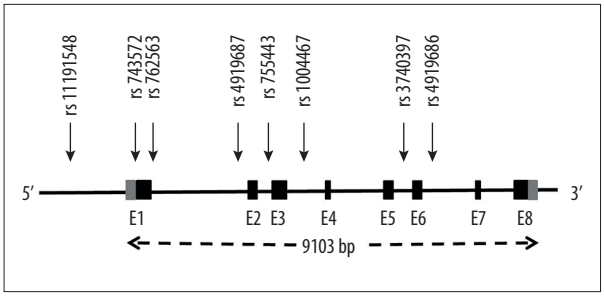

Figure 1. *CYP17A1* (cytochrome P450, family 17, subfamily A, polypeptide 1) structure and relative position of 8 tag SNPs. Black boxes indicate exons, lines indicate introns, and gray boxes indicate 5'-UTR and 3'-UTR.

differences in BP levels among different genotype and allele groups with age, sex, and body mass index (BMI) as covariates. Logistic regression analysis was applied to test the association between each SNP and hypertension risk. In genetic model analyses (co-dominant, dominant, recessive, overdominant, and additive), the minor allele of each SNP was regarded as the risk factor, and each analysis was adjusted by age, gender, and BMI. Linkage disequilibrium (LD) analysis was performed in the case and control groups using SHEsis software online (*http://analysis.bio-x.cn/myAnalysis.php*). To explore whether these five variants had combined effects on hypertension, haplotype analysis was also performed by using SHEsis software. The Bonferroni correction was applied to assess the probability of a spurious association by multiple comparisons (P<0.05/5). A 2-tailed probability value of P<0.05 was considered as statistically significant. All analyses were carried out by using SPSS (version 16.0; SPSS Inc., Chicago, Illinois, USA) and adjusted for age, sex, and BMI.

Bioinformatics analysis

P-match is a kind of functional prediction tool (*http://www.generegulation.com/cgi-bin/pub/programs/pmatch/bin/pmatch.cgi*), which is used to predict the effects of polymorphisms on the sequence structures of potential binding sites for transcription factors (TFs). This software is involved with a library of mononucleotide weight matrices as well as sets of aligned known TF binding sites from TRANSFACR. The available TF binding sites around the SNPs localized in the promoter and intron region of the target gene are considered in this software.

Human splicing finder (HSF) software, a kind of Bioinformatics tool (*http://www.umd.be/HSF/*), is used to predict the effects of mutations on splicing signals and to identify splicing motifs in any human sequence. This software contains all the genes and alternative transcripts, as well as intronic sequences extracted from the Ensembl human genome database, to study the potential effects of SNPs on splicing.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 2. Oligonucleotides and restriction enzymes of polymorphic sites for genotyping.

Locus	Location	Long PCR		Nest PCR		Restriction enzyme	Digested bands (bp)
		Primer sequence (5'–3')	TA	Primer sequence (5'–3')	TB		
rs4919686	Intron6	F: GTCAGGGACAGAAGTATGGC	56°C	F: TGACCGTAACCGTCTCCTC	56°C	NmuCI	A: 122, 208; C: 330
		R: TGGATGAGTCAATGCGTGT	56°C	R: GCTGGTCTTGAACCCCTG	56°C		
rs3740397	Intron5	F: GTCAGGGACAGAAGTATGGC	56°C	F: AACCACATTCTCACCACCATAG	57°C	MunI	G: 172, 75; C: 247
		R: TGGATGAGTCAATGCGTGT	56°C	R: GGGTCAAAGCCAACTACTGC	57°C		
rs1004467	Intron3	F: GAGTTGCCTTCCTGTGGTC	56°C	F: CTGTCTTCGTGGCGGTAAC	56°C	RsaI	T: 19, 193 C: 212
		R: CAGCGATGAATGCGTATAGA	56°C	R: GGGGACAATGTCAGGGTGT	56°C		
rs755443	Intron2	F: GAGTTGCCTTCCTGTGGTC	56°C	F: CAAGGATGGCGATCAGAAG	56°C	HapII	G: 190,20 A: 210
		R: CAGCGATGAATGCGTATAGA	56°C	R: CAGTTGCCTCTTAACAGGACC	56°C		
rs4919687	Intron1	F: GAGTTGCCTTCCTGTGGTC	56°C	F: AGGGTCTGTCCTACCAAGTCC	57°C	Kpn I	C: 153, 81; T: 234
		R: CAGCGATGAATGCGTATAGA	56°C	R: AGAGTCAGCGAAGGCGATAC	57°C		
rs762563	Exon1	F: CCCTGAAATGTCATTGTAGAAA	56°C	F: GGGGTACTTGGCACCATG	56°C	Nco I	C: 16,177; G: 193
		R: CCCAGATACCATTCGCACT	56°C	R: GTCAAGGTGAAGATCAGGGTAG	56°C		
rs743572	5' UTR	F: CCCTGAAATGTCATTGTAGAAA	56°C	F: GCAGGCAAGATAGACCGC	56°C	Acc II	C: 194,7 T: 211
		R: CCCAGATACCATTCGCACT	56°C	R: AGTTGAGCCAGCCCTTGA	56°C		
rs11191548	5'near	F: TTCTTGTTACGGGAGGTGC	56°C	F: TGCAGGGTTGCTCTGGTA	56°C	Tai I	C: 65,276 T: 341
		R: TGAGAAGACCATTCTGCCAC	56°C	R: ACCACGAATAGCCTGAGACA	56°C		

F – forward primer; R – reverse primer; T^A – temperature of long-PCR annealing; T^B – the temperature of nest-PCR annealing.

Results

Population characteristics

The general characteristics of the study subjects are summed up in Table 3. The distribution of age and gender showed no significant difference between the case and control groups, whereas the BP and BMI levels were significantly higher in the patient group than in the control group. As the development of hypertension would be affected by multiple confounding factors, the confounding factors (including gender, age, and BMI) were adjusted as covariants in the further analyses.

The genotype distributions of eight SNPs in the case-control groups are described in Table 4. Of the eight variants examined in the total population, six showed no indication of a deviation from Hardy-Weinberg equilibrium in normotensive controls (P>0.05). Because the minor allele frequency of rs755443 was 0 in the control group, leading to the inaccurate results for analysis, this SNP was also ruled out for the further analysis. Genotyping was successfully done for 504 out of the 510 (98.8%) EH patients and for 505 out of the 510 (99.0%) controls.

Single-site analyses

The results of single-site analyses for the five SNPs localized in the *CYP17A1* region are shown in Tables 5–7. The minor allele-T rate of rs4919687 (P=0.0202, OR=1.283) was found to be significantly greater in the patient group than in the control group, and the minor allele-T of rs4919687 (mean difference [MD]=3.045, P=0.0106) was also found to be significantly associated with increased SBP levels. However, the minor allele-C frequency of rs11191548 (P=0.0002, OR=0.675) was found to be significantly smaller in the patient group than in the control group, and the minor allele-C of rs11191548 was also found to be significantly associated with decreased BP levels (MD_{SBP}=–3.354, P_{SBP}=0.0041, MD_{DBP}=–1.917, P_{DBP}=0.0066) (Table 5).

The differences in BP levels among the groups with different genotypes were analyzed by ANCOVA with multiple comparison correction, and the results are shown in Table 6. Via adjusting for age, gender, and BMI, the SBP level of the subjects with CT+TT genotype of rs4919687 was significantly higher than that of the subjects with CC genotype (P_{SBP}=0.002), before or after Bonferroni correction. Indeed, the carriers with T alleles had higher SBP levels compared with those with the CC

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 3. The basic characteristics of the Yunnan Han Chinese population.

Parameters	Normotensive	Hypertensive	*p*-value
Number	510.00	510.00	---
Males (%)	65.69	65.69	1.000
Age (years)	53.46±10.44	53.81±10.23	0.588
Current smokers (%)	38.82	37.84	0.747
Current drinkers (%)	26.47	27.45	0.724
SBP (mm HG)	111.5±11.09	147.92±20.67	<0.001
DBP (mm HG)	73.53±7.07	94.75±13.04	<0.001
BMI (Kg/m^2)	22.98±2.79	24.64±2.81	<0.001

SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index. Data were presented as mean±standard deviation. *p*-value was calculated on comparison on hypertension cases and controls and $p<0.05$ was considered statistical significance.

Table 4. Exact test for Hardy-Weinberg equilibrium (n=1009).

Region	Variant	Allele *1/2	Case-hypertensive					Control-normotensive				
			MAF	1/1	1/2	2/2	*p*-value	MAF	1/1	1/2	2/2	*p*-value
Intron_6	rs4919686	A/C	0.170	348	141	15	0.871	0.144	370	125	10	1
Intron_5	rs3740397	C/G	0.480	142	240	122	0.332	0.505	127	246	132	0.590
Intron_3	rs1004467	T/C	0.361	244	156	104	<0.0001	0.432	197	180	128	<0.0001
Intron_2	rs755443	G/A	0.031	475	27	2	0.074	0.000	499	6	0	1
Intron_1	rs4919687	C/T	0.273	261	211	32	0.260	0.245	292	179	34	0.401
Exon_1	rs762563	C/G	0.003	502	1	1	0.003	0.004	503	0	2	<0.0001
5' UTR	rs743572	C/T	0.439	163	240	101	0.473	0.416	177	236	92	0.411
5' near	rs11191548	T/C	0.241	280	205	19	0.014	0.305	243	216	46	0.920

MAF – minor allele frequency. *p*-value >0.05 was considered to be consistent with Hardy-Weinberg equilibrium. * 1 represented major allele, 2 represented minor allele.

Table 5. The associations between minor-alleles of *CYP17A1* SNPs and the risk of EH and BP levels.

SNP	Allele *1/2	MAF		Risk of minor allele			SBP			DBP		
		Control	Case	OR**	95% CI**	*p***	MD**	95% CI**	*p***	MD**	95% CI**	*p***
rs4919686	A/C	0.144	0.170	1.298	1.008–1.673	0.0435	2.657	–0.157–5.471	0.0642	0.550	–1.150–2.250	0.5256
rs3740397	C/G	0.505	0.480	0.886	0.738–1.064	0.1959	–1.038	–3.082–1.006	0.3194	–1.273	–2.506–(–0.040)	0.0430
rs4919687	C/T	0.245	0.273	1.283	1.040–1.583	**0.0202**	3.045	0.712–5.378	**0.0106*** **	0.976	–0.434–2.386	0.1748
rs743572	C/T	0.416	0.439	1.096	0.911–1.318	0.3308	0.713	–1.351–2.778	0.4980	1.321	0.076–2.566	0.0376
rs11191548	T/C	0.305	0.241	0.675	0.549–0.830	**0.0002*** **	–3.354	–5.642–(–1.066)	**0.0041*** **	–1.917	–3.299–(–0.536)	**0.0066*** **

SBP – systolic blood pressure; DBP – diastolic blood pressure; MAF – minor allele frequency; MD – mean difference. MD and 95% confidence intervals (CI) were analyzed by ANCOVA between the groups with different alleles; odds ratio (OR) and 95% CI were analyzed by logistic regression between the case and control groups; $p<0.05$ was considered statistical significance. * 1 represented major allele, 2 represented minor allele; ** adjusted for sex, age and BMI; *** indicated that the *p*-value remained significant after Boferroni correction ($p<0.05/5$).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 6. The associations of 5 SNPs with the BP levels in this population.

SNP	Genotype	N	SBP*	*p*-value*	DBP*	*p*-value*
rs4919686	AA	718	128.91±24.54		83.73±14.84	
	AC+CC	291	131.93±23.59	0.064	84.33±14.26	0.547
rs3740397	CC	269	132.09±24.01		85.88±14.47	
	CG+GG	740	129.02±24.13	0.067	83.23±14.53	0.080
rs4919687	CC	553	127.69±24.15		83.42±14.63	
	CT+TT	456	132.34±23.85	**0.002****	85.04±14.46	0.071
rs743572	CC	340	129.64±23.90		83.04±14.42	
	CT+TT	669	129.90±24.26	0.870	84.35±14.64	0.163
rs11191548	TT	523	131.17±24.13		85.04±14.57	
	TC+CC	486	128.10±23.94	**0.038**	83.19±14.46	**0.037**

SBP – systolic blood pressure; DBP – diastolic blood pressure. Continuous variables were expressed as the mean ±S.D. *p*-value <0.05was considered statistical significance. * Adjusted for age, gender and BMI; ** indicated that the *p*-value remained significant after Bonferroni correction.

genotype, which implied that individuals who carried the T allele of rs4919687 might be more susceptible to EH. Although there was a significant association of rs11191548 polymorphism (P_{SBP}=0.038, P_{DBP}=0.037) with SBP and DBP levels, these positive correlations did not exist after Bonferroni correction.

In order to find a comprehensive view of the effects mediated by the genetic factors on the development of EH, different genetic models were used to identify the associations between these polymorphisms and the risk of EH (Table 7). After adjustment by age, sex, and BMI, the SNP rs4919687 was found to be significantly associated with hypertension risk (dominant: OR=1.47, 95% CI=1.13–1.92, P=0.0038), and the rs11191548 was also found to be significantly associated with hypertension risk (codominant model: P=0.0001, TC *vs.* TT: OR=0.76, 95% CI=0.58–1.00, CC *vs.* TT: OR=0.31, 95% CI=0.17-0.55; dominant: OR=0.68, 95 CI%=0.52–0.88, P=0.0036; recessive: OR=0.35, 95% CI=0.19–0.62, P=0.0002; log-additive: OR=0.66, 95% CI=0.53–0.81, P=0.0001). These results remained statistically significant via Bonferroni correction.

Linkage disequilibrium analysis

Linkage disequilibrium (LD) analysis demonstrated that two SNPs (rs11191548 and rs4919687) were in LD in both control (/D'/=0.82) and case (/D'/=0.92) groups (Figures 2, 3).

Bioinformatics analyses

Seven SNPs (including rs11191548, rs743572, rs4919687, rs755443, rs1004467, rs3740397, and rs4919686) excluding the exonic polymorphisms of the *CYP17A1* gene were further analyzed for the influence on the sequence structures of TF binding sites by p-match. The results indicated that the sequence (AGGCAGGTACCTG) containing the major allele G of rs4919687 (c.298-99C>T) could be captured by the TF AREB6, while the sequence (AGGCAAGTACCTG) containing the minor allele A of rs4919687 could not be captured by the TF AREB6, suggesting that the single nucleotide substitution of G→A at position 298–299 in intron 1 of the *CYP17A1* gene could change the sequence structure of the TF binding site. No TF binding site was found around the *loci* rs11191548, rs743572, rs755443, rs3740397, and rs4919686.

These SNPs (rs762563, rs4919687, rs755443, rs1004467, rs3740397, rs4919686) localized in the exons or introns of the *CYP17A1* gene were also analyzed for the effects on the process of mRNA splicing by HSF software. The results revealed that the rs4919687 (c.298-99C>T) polymorphism localized at position 298-299 of intron 1 of *CYP17A1* led to the destruction of ESS (including ESR and Motif 3) sites; the rs755443 (c.437-83C>T) polymorphism localized in intron 2 of *CYP17A1* led to the creation of ESE (EIEs and ESR) sites, possibly enhancing the process of splicing; the rs762563 (c.66C>G) polymorphism localized at the 66 nucleotide of exon 1 of *CYP17A1* led to the creation of the new exonic splicing silencer (ESS, including Motif 2, Fas, IIEs, ESR) sites and the destruction of the exonic splicing enhancer (ESE, including SC35, EIEs, SF2/ASF(Ig)) sites, thereby weakening the process of splicing.

Haplotype analyses

The summarized results of haplotype analyses for the combined effect of rs4919686, rs3740397, rs4919687, rs743572, and rs11191548 in the Yunnan Han Chinese population are shown in Table 8. Twenty-three haplotypes of the *CYP17A1* gene were

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 7. The associations of 5 SNPs with the hypertension risk in this population.

SNP	Allele *1/2	Model	Genotype status	n=1009	
				OR** (95% CI)	*p***-value
rs4919686	A/C	Codominant	1/1	1.00	0.1300
			1/2	1.29 (0.96–1.73)	
			2/2	1.77 (0.75–4.18)	
		Dominant	1/1	1.00	0.0580
			1/2–2/2	1.32 (0.99–1.76)	
		Recessive	1/1–1/2	1.00	0.2400
			2/2	1.65 (0.70–3.87)	
		Overdominant	1/1–2/2	1.00	0.1200
			1/2	1.26 (0.94–1.69)	
		Log-additive	---	1.30 (1.01–1.68)	0.0430
rs3740397	C/G	Codominant	1/1	1.00	0.4100
			1/2	0.85 (0.62–1.16)	
			2/2	0.79 (0.55–1.14)	
		Dominant	1/1	1.00	0.2100
			1/2–2/2	0.83 (0.62–1.11)	
		Recessive	1/1–1/2	1.00	0.4100
			2/2	0.88 (0.65–1.19)	
		Overdominant	1/1–2/2	1.00	0.6800
			1/2	0.95 (0.73–1.23)	
		Log-additive	---	0.89 (0.74–1.07)	0.2000
rs4919687	C/T	Codominant	1/1	1.00	**0.0100*****
			1/2	1.53 (1.16–2.01)	
			2/2	1.20 (0.70–2.05)	
		Dominant	1/1	1.00	**0.0038*****
			1/2–2/2	1.47 (1.13–1.92)	
		Recessive	1/1–1/2	1.00	0.9900
			2/2	1.00 (0.59–1.69)	
		Overdominant	1/1–2/2	1.00	0.0320
			1/2	1.50 (1.14–1.96)	
		Log-additive	---	1.29 (1.04–1.59)	0.0190

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 7 continued. The associations of 5 SNPs with the hypertension risk in this population.

SNP	Allele *1/2	Model	Genotype status	n=1009	
				OR** (95% CI)	*p***-value
rs743572	C/T	Codominant	1/1	1.00	0.5800
			1/2	1.15 (0.86–1.54)	
			2/2	1.18 (0.81–1.70)	
		Dominant	1/1	1.00	0.3000
			1/2–2/2	1.16 (0.88–1.52)	
		Recessive	1/1–1/2	1.00	0.6200
			2/2	1.09 (0.78–1.51)	
		Overdominant	1/1–2/2	1.00	0.5600
			1/2	1.08 (0.83–1.40)	
		Log-additive	---	1.09 (0.91–1.31)	0.3400
rs11191548	T/C	Codominant	1/1	1.00	**0.0001*** **
			1/2	0.76 (0.58–1.00)	
			2/2	0.31 (0.17–0.55)	
		Dominant	1/1	1.00	**0.0036*** **
			1/2–2/2	0.68 (0.52–0.88)	
		Recessive	1/1–1/2	1.00	**0.0002*** **
			2/2	0.35 (0.19–0.62)	
		Overdominant	1/1–2/2	1.00	0.2600
			1/2	0.86 (0.66–1.12)	
		Log-additive	---	0.66 (0.53–0.81)	**0.0001*** **

OR – odd ratio; CI – confidence interval. Note: OR and 95% CI was calculated by logistic regression analysis model; *p*-value<0.05 was considered statistical significance. * 1 represented major allele, 2 represented minor allele; ** estimated by logistic regression analysis adjusted for sex, age and BMI; *** Indicated that the *p*-value remained significant after Bonferroni correction.

constructed, but only eight of them had a frequency above 1% in the case and control groups. The results showed that the frequency of haplotype 1 (H1 ACCTT) was higher than that of the other haplotypes. Thus, taking H1 as a reference, the relative risk of EH related to different haplotypes was evaluated by logistic analyses. After adjusting for sex, age, and BMI, H2 AGCCC (P=0.0014, OR=0.68) displayed a significant association with decreased risk of EH; the H6 AGTCT (P=0.0013, OR=4.27) had a significant association with increased risk of EH. These results remained statistically significant via Bonferroni corrections.

Discussion

Hypertension is a main factor causing high rates of global morbidity and mortality [1]. The *CYP17A1* gene is emerging as a risk factor for EH [33,34]. Since there are limited data on the *CYP17A1* genetic determinants of EH for the patients among the Han Chinese population in Yunnan province, our study sought to determine the contribution of eight SNPs localized in the *CYP17A1* gene region (including rs743572, rs1004467, rs4919687, rs755443, rs3740397, rs4919686, rs762563, and rs11191548) in inducing susceptibility to EH in this population. We found that (1) among the Chinese Han population in Yunnan province the rs11191548 and rs4919687 SNPs were significantly associated with EH, and these two polymorphisms were found in linkage disequilibrium; (2) in the bioinformatics analyses, the rs4919687 polymorphism was found to cause the destruction of exonic splicing silencer (including ESR and Motif 3) sites and to transform the sequence structure of the transcription factor AREB6 binding site, respectively, thereby functionally affecting the expression level

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

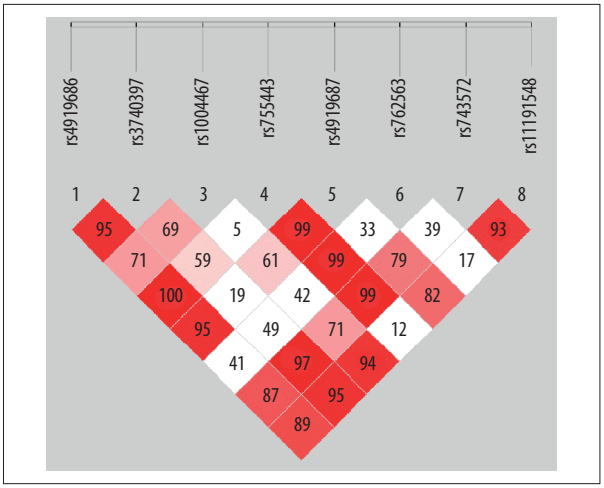

Figure 2. Linkage disequilibrium analysis of SNPs localized in the *CYP17A1* gene in the control group. The rs11191548 and rs4919687 were in linkage disequilibrium (/D'/=0.82) in the control group.

Figure 3. Linkage disequilibrium analysis of SNPs localized in the *CYP17A1* gene in the case group. The rs11191548 and rs4919687 were in linkage disequilibrium (/D'/=0.92) in the case group.

Table 8. Associations between the *CYP17A1* gene haplotypes and the hypertension risk in this population.

Name	Haplotype	n=1009		
		Frequence	OR (95 CI%)	*p*-value
H1	ACCTT	0.3977	1.00	---
H2	AGCCC	0.2558	0.68 (0.53–0.86)	**0.0014***
H3	CGTCT	0.1454	1.17 (0.87–1.56)	0.3000
H4	ACTCT	0.0734	0.95 (0.66–1.38)	0.7900
H5	AGCCT	0.0597	0.87 (0.58–1.29)	0.4800
H6	AGTCT	0.0176	4.27 (1.77–10.29)	**0.0013***
H7	ACTTT	0.0119	0.66 (0.25–1.74)	0.4000
H8	ACCCT	0.0116	1.69 (0.68–4.22)	0.2600

CI – confidence interval; OR – odds ratio; SNP – single-nucleotide polymorphism. Note: The SNP order of constructing haplotype was as follows: rs4919686(A/C), rs3740397(C/G), rs4919687(C/T), rs743572(C/T), rs11191548(T/C); OR and 95% CI were calculated by a haplotype-based logistic regression analysis. Haplotypes with frequencies<0.01 were not included in this table; *p*-value<0.05 was considered statistical significance. * Indicated that the *p*-value remained significant after Bonferroni correction (p<0.05/8).

of the *CYP17A1* gene; and (3) the haplotype-rs4919686A, rs3740397G, rs4919687C, rs743572C, rs11191548C and haplotype-rs4919686A, rs3740397G, rs4919687T, rs743572C, rs11191548T were found to be susceptible to EH among the Han Chinese population in Yunnan province.

Several reports have investigated the relationship of the rs11191548 polymorphism (g.111886A>G) to the development of EH among different populations. Most of those studies claimed that the T allele of rs11191548 might be a risk factor for EH. Two large-scale GWAS studies among European ancestry from the Global BPgen consortium and CHARGE consortium identified that the allele-T of rs11191548 was significantly associated with increased hypertension risk and BP levels [10,12]. An associated study conducted in Europeans also found that minor alleles-C of rs11191548 were associated with a lower probability of orthostatic hypotension [18]. Research among Japanese [13] and Korean [15] populations indicated that individuals carrying the allele-T of rs11191548 experienced significantly increased BP levels and hypertension risk compared to the respective non-carriers. A recent hypertension study among East Asians also exhibited the significant association between the T-allele of this polymorphism and the increased hypertension risk and BP levels [20,22,24]. However, other related studies

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

argued against them and indicated that the rs11191548 C-allele might be a risk factor for EH. A study among the Shanghai Han Chinese population found that the risk C-allele was associated with increased SBP levels and increased hypertension risk (in an additive genetic model) [21]. Another study conducted in the adult She ethnic minority from Ningde City in Fujian province of China came to the same conclusion [23]. In our present study, by adjusting for age, gender, and BMI, the minor C-allele of rs11191548 was found to be significantly associated with decreased EH risk and BP levels, and the subjects with TC+CC genotypes were found to have lower EH risk and BP levels than the subjects with TT genotype. Indeed, individuals who carried the C allele of rs11191548 could be less susceptible to EH among the Yunnan Han population. Our finding among the Yunnan Han Chinese population was in accordance with the reports of Newton-Cheh et al. [10,12,13,15,18,20,22,24]. However, this result was in contrast to what Li et al. [21,23] found in their study. This inconsistency could be attributed to the different genetic backgrounds, living habits, and environmental factors among different populations. It was not hard to see that people from different ethnic groups or just from different regions in the same country could also demonstrate certain genotype differences. Even though the researches were conducted in one country, our study conducted in the Yunnan Han Chinese population was in contrast to the She population in Fujian [23] and the Han population in Shanghai [21].

Detection of intron 1 rs4919687 (c.298-99C>T) polymorphism in our samples indicated that the minor T-allele and TT+CT genotype of this polymorphism were found to be significantly associated with the increased risk of EH and level of SBP among the Yunnan Han Chinese population. Indeed, the T-allele of this polymorphism seemed to be a risk factor for EH in this population. To date, only a little is known about the association of this polymorphism with EH. The TC genotype of rs4919687 was found to be a protective genetic marker for EH among the Uighur population [36]. Previous studies have shown that the polymorphisms localized in the introns and exons close to the splice site would have effects on the process of mRNA splicing [37]. In the bioinformatics analysis, it was observed that the c.298-99C>T (rs4919687) led to the destruction of ESS (including ESR and Motif 3) sites, thereby enhancing the process of splicing. It was also known that the SNPs localized in regulatory regions within introns or in the regions between genes were called regulatory SNPs, and that these regulatory SNPs affected gene regulation by changing transcription factor (TF) binding affinities to genomic sequences [38]. Also, the functional effect of this intronic polymorphism on the expression level of the *CYP17A1* gene was predicted by p-match. The result indicated that the single nucleotide substitution of G→A at position 298–299 in intron 1 of *CYP17A1* could transform the sequence structure of the TF AREB6 binding site, thereby influencing TF AREB6 binding affinities to its binding site localized in this gene. Taken together, our findings suggested that the C→T single nucleotide substitution of the intronic polymorphism rs4919687 was strongly associated with EH in our samples by affecting the process of *CYP17A1* mRNA splicing and by changing binding affinity with TF AREB6.

The rs743572 (c.-34T>C) was localized at the 5' untranslated region of the *CYP17A1* gene. Currently, the relation of rs743572 polymorphism and EH has not been clarified domestically or abroad. An associated study among European ancestry participants from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium indicated that polymorphism rs743572 was associated with BP traits [39]. Another recent study conducted in patients with arterial hypertension and cardiac left ventricular ejection fraction revealed that no significant association was found between SNP rs743572 and mean 24-h systolic or diastolic BP [40]. In our study, no association was observed between this polymorphism and EH among the Han Chinese population.

The polymorphism rs1004467 (c.666+35T>C) localized in intron 3 of the *CYP17A1* gene has been investigated in lots of association studies of complex polygenic disease. Several hypertensive association studies among Japanese [17] and Shanghai Han Chinese [20] have reported that the minor allele-A of rs1004467 could be a risk factor for EH. On the contrary, insignificant associations with EH or BP traits were reported in the populations of Beijing Chinese children [25] and of Han and Uighur in Xinjiang province of China [36]. In our study, no association was observed between this polymorphism and EH among the Han Chinese population in Yunnan province. The failure to find an association among our study sample could be attributed to the insufficient sample size. Further study in a larger sample size from the Yunnan Han Chinese population is needed to identify its relationship with EH. The bioinformatics analyses found that the sequence (CTAGTAGACC) containing the major/minor allele of rs1004467 could be captured by the TF c-Rel, but this mutation could not affect the binding affinity between this TF c-Rel and its binding site.

In recent years, there were only a few studies about the interactions between two polymorphisms, i.e., rs4919686 (1139+19T>G) and rs3740397 (969+75C>G), and occurrence of complex diseases. The AC genotype of rs4919686 was found to be a protective genetic marker for EH among the Uighur population [36]. Our present study among Han Chinese populations showed no association of these two polymorphisms with EH.

Regarding rs755443 (c.437-83C>T) and rs762563 (c.66C>G) polymorphisms, no studies have been reported about these two variants. Our present study among the Yunnan Han Chinese population showed no association of these two polymorphisms with EH.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

In order to enhance the study power, haplotype analysis was performed. Few studies have been done to investigate the effects of haplotypes localized in the *CYP17A1* gene on EH. An associated study conducted among the Uighur population indicated that the distributions of the haplotypes established by rs4919686–rs4919687, rs4919686–rs10786712, rs4919686–rs4919687–rs2486758, and rs4919686–rs10786712–rs2486758 were significantly different between the EH patients and control subjects [36]. In our present study, H2 (rs4919686A, rs3740397G, rs4919687C, rs743572C, rs11191548C) was found to significantly decrease the risk of EH and seemed to be protective, whereas H6 (rs4919686A, rs3740397G, rs4919687T, rs743572C, rs11191548T) was found to significantly increase the risk of EH and seemed to be risky. Indeed, the risk effect of rs4919687-T was shown in haplotype H6 and not shown in H2, whereas the protective effect of rs11191548-C was shown in H2 and not shown in H6. Coincidentally, H6 showed a significant association with the increased risk of EH, whereas H2 showed a significant association with the decreased risk of EH. The result of linkage disequilibrium analysis, that the rs11191548 and rs4919687 were found in linkage disequilibrium in both control and case groups among the Yunnan Chinese Han population, was in accordance with the haplotype analysis. Indeed, these two analyses suggested an additive effect of the rs11191548 and rs4919687 polymorphisms.

It is tempting to suggest that the mutations of the *CYP17A1* gene might be a genetic risk factor for EH among the Chinese Han population. Indeed, cytochrome P450C17 (steroid 17α-hydroxylase/17, 20-lyase; EC 1.14.99.9) is a single microsomal enzyme, which has catalytic activities for the synthesis of mineralocorticoids and sex steroids, respectively [41]. Human expression of CYP17A1 in the fasciculate pregnenolone is converted into 17α-hydroxypregnenolone, which is oxidized to 17α-hydroxyprogesterone by 3β-hydroxysteroid dehydrogenase, followed by 21-hydroxylation by CYP21A2 to 11-deoxycortisol. 11-Deoxycortisol and 11-deoxycorticosterone then enter the mitochondria, where they are acted upon by the CYP11B1 enzyme that is specific to the zona Fasciculata to generate cortisol and corticosterone, specifically [42]. The single nucleotide polymorphism of the *CYP17A1* gene may lead to deficiency of the P450C17 enzyme activity, which forces steroidogenesis to corticosterone rather than cortisol via 11-deoxycorticosterone, which in human beings is normally a very minor adrenal product. 11-Deoxycorticosterone, however, is a kind of mineralocorticoid, which is slightly less potent than aldosterone [30]. The state of mineralocorticoid 11-deoxycorticosterone excess is characterized by hypertension, hypokalemia, suppressed plasma renin activity, and low aldosterone concentrations [43]. As both renin and aldosterone play vital roles in the renin-angiotensin-aldosterone system (RAAS), SNPs in this gene might result in a suppressed RAAS characterized by abnormal blood pressure [44]. Taken together, our findings suggested that these two *CYP17A1* polymorphisms rs11191548 and rs4919687 being in linkage disequilibrium could be a risk factor for EH among the Yunnan Han Chinese population, which provided new insights into the genetics and biology of blood pressure, and pointed out potential novel therapeutic pathways for cardiovascular disease prevention.

Some potential limitations of our study should be noted. Firstly, we did not collect data on antihypertensive medicine levels and drug compliance. Secondly, this study was limited by the relatively small sample size; a large number of clinical samples are needed in future studies.

Conclusions

In conclusion, this is the first study to investigate the contribution of CYP17A1 variants in inducing the susceptibility to EH among the Southwest Han Chinese Population in Yunnan province, and is the first haplotype-based case-control study to correlate its association with EH. Two polymorphisms, i.e., rs11191548 and rs4919687, of the *CYP17A1* gene were found to be significantly associated with EH in the Yunnan Han population of China. The C-allele of rs11191548 could be a protective genetic marker for EH, and the T-allele of rs4919687 could be a risk genetic marker for EH among this population. However, future studies should be performed with a large sample size.

Acknowledgements

We are grateful to Dr. Jing Du for advice in revising this paper and Dr. Keming Zhu for helpful discussion and advice in revising this paper. We are also grateful to all the patients participating in this study.

Conflicts of interest

The authors declare that they have no competing interests.

Statement

This study was approved by the ethics committee of the School of Medicine of Yunnan University. Informed consent was obtained from all individual participants included in the study, and the consent authorization for publication was on file.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

References:

1. Guilbert JJ: The world health report 2002 – reducing risks, promoting healthy life. Educ Health (Abingdon), 2003; 16: 230
2. Kearney PM, Whelton M, Reynolds K et al: Global burden of hypertension: analysis of worldwide data. Lancet, 2005; 365: 217–23
3. Lawes CM, Vander Hoorn S, Rodgers A: Global burden of blood-pressure-related disease, 2001. Lancet, 2008; 371: 1513–18
4. Wu Y, Huxley R, Li L et al: Prevalence, awareness, treatment, and control of hypertension in China: Data from the China National Nutrition and Health Survey 2002. Circulation, 2008; 118: 2679–86
5. Whelton PK, He J, Appel LJ et al: Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. JAMA, 2002; 288: 1882–88
6. Garcia EA, Newhouse S, Caulfield MJ, Munroe PB: Genes and hypertension. Curr Pharm Des, 2003; 9: 1679–89
7. Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature, 2007; 447: 661–78
8. Sabatti C, Service SK, Hartikainen AL et al: Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. Nat Genet, 2009; 41: 35–46
9. Elbekai RH, El-Kadi AO: Cytochrome P450 enzymes: Central players in cardiovascular health and disease. Pharmacol Ther, 2006; 112: 564–87
10. Newton-Cheh C, Johnson T, Gateva V et al: Genome-wide association study identifies eight *loci* associated with blood pressure. Nat Genet, 2009; 41: 666–76
11. Levy D, Ehret GB, Rice K et al: Genome-wide association study of blood pressure and hypertension. Nat Genet, 2009; 41: 677–87
12. Ehret GB, Munroe PB, Rice KM et al: Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature, 2011; 478: 103–9
13. Takeuchi F, Isono M, Katsuya T et al: Blood pressure and hypertension are associated with 7 *loci* in the Japanese population. Circulation, 2010; 121: 2302–9
14. Hamrefors V, Sjogren M, Almgren P et al: Pharmacogenetic implications for eight common blood pressure-associated single-nucleotide polymorphisms. J Hypertens, 2012; 30: 1151–60
15. Hong KW, Jin HS, Lim JE et al: Recapitulation of two genomewide association studies on blood pressure and essential hypertension in the Korean population. J Hum Genet, 2010; 55: 336–41
16. Yang SJ, Lee ST, Kim WJ et al: Genetic variation in CYP17A1 is associated with arterial stiffness in diabetic subjects. Exp Diabetes Res, 2012; 2012: 827172
17. Tabara Y, Kohara K, Kita Y et al: Common variants in the ATP2B1 gene are associated with susceptibility to hypertension: The Japanese Millennium Genome Project. Hypertension, 2010; 56: 973–80
18. Fedorowski A, Franceschini N, Brody J et al: Orthostatic hypotension and novel blood pressure-associated gene variants: Genetics of Postural Hemodynamics (GPH) Consortium. Eur Heart J, 2012; 33: 2331–41
19. Ganesh SK, Tragante V, Guo W et al: *Loci* influencing blood pressure identified using a cardiovascular gene-centric array. Hum Mol Genet, 2013; 22: 1663–78
20. Liu C, Li H, Qi Q et al: Common variants in or near FGF5, CYP17A1 and MTHFR genes are associated with blood pressure and hypertension in Chinese Hans. J Hypertens, 2011; 29: 70–75
21. Li X, Ling Y, Lu D et al: Common polymorphism rs11191548 near the CYP17A1 gene is associated with hypertension and systolic blood pressure in the Han Chinese population. Am J Hypertens, 2013; 26: 465–72
22. Xi B, Shen Y, Reilly KH et al: Recapitulation of four hypertension susceptibility genes (CSK, CYP17A1, MTHFR, and FGF5) in East Asians. Metabolism, 2013; 62: 196–203
23. Lin Y, Lai X, Chen B et al: Genetic variations in CYP17A1, CACNB2 and PLEKHA7 are associated with blood pressure and/or hypertension in She ethnic minority of China. Atherosclerosis, 2011; 219: 709–14
24. Wu L, Xi B, Zhang M et al: A sex-specific effect of the CYP17A1 SNP rs11191548 on blood pressure in Chinese children. J Hum Hyperten, 2012; 26: 731–36
25. Xi B, Shen Y, Zhao X et al: Association of common variants in/near six genes (ATP2B1, CSK, MTHFR, CYP17A1, STK39 and FGF5) with blood pressure/hypertension risk in Chinese children. J Hum Hypertens, 2014; 28: 32–36
26. Picado-Leonard J, Miller WL: Cloning and sequence of the human gene for P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): Similarity with the gene for P450c21. DNA, 1987; 6: 439–48
27. Zuber MX, Simpson ER, Waterman MR: Expression of bovine 17 alpha-hydroxylase cytochrome P-450 cDNA in nonsteroidogenic (COS 1) cells. Science, 1986; 234: 1258–61
28. Liu BL, Qiao J, Chen X et al: [Clinical and molecular genetic analysis for 7 patients from 5 pedigrees with 17a-hydroxylase/17, 20 lyase deficiency]. Zhonghua yi xue yi chuan xue za zhi, 2009; 26: 282–87 [in Chinese]
29. Han B, Xue L, Fan M et al: Clinical and molecular manifestation of fifteen 17OHD patients: A novel mutation and a founder effect. Endocrine, 2016; 53: 784–90
30. Auchus RJ: Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic. J Steroid Biochem Mol Biol, 2016 [Epub ahead of print]
31. Zhang M, Sun S, Liu Y et al: New, recurrent, and prevalent mutations: Clinical and molecular characterization of 26 Chinese patients with 17alpha-hydroxylase/17,20-lyase deficiency. J Steroid Biochem Mol Biol, 2015; 150: 11–16
32. Turkkahraman D, Guran T, Ivison H et al: Identification of a novel large CYP17A1 deletion by MLPA analysis in a family with classic 17alpha-hydroxylase deficiency. Sex Dev, 2015; 9: 91–97
33. Kagimoto M, Winter JS, Kagimoto K et al: Structural characterization of normal and mutant human steroid 17 alpha-hydroxylase genes: molecular basis of one example of combined 17 alpha-hydroxylase/17,20 lyase deficiency. Mol Endocrinol, 1988; 2: 564–70
34. Dhir V, Reisch N, Bleicken CM et al: Steroid 17alpha-hydroxylase deficiency: functional characterization of four mutations (A174E, V178D, R440C, L465P) in the CYP17A1 gene. J Clin Endocrinol Metab, 2009; 94: 3058–64
35. Whitworth JA: 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens, 2003; 21: 1983–92
36. Dai CF, Xie X, Ma YT et al: Relationship between CYP17A1 Genetic Polymorphism and Essential Hypertension in a Chinese Population. Aging Dis, 2015; 6: 486–98
37. Liu Q, Wang Z, Wu Y et al: Five novel mutations in the ADAR1 gene associated with dyschromatosis symmetrica hereditaria. BMC Med Genet, 2014; 15: 69
38. Zuo C, Shin S, Keles S: atSNP: Transcription factor binding affinity testing for regulatory SNP detection. Bioinformatics, 2015; 31: 3353–55
39. Morrison AC, Bis JC, Hwang SJ et al: Sequence analysis of six blood pressure candidate regions in 4,178 individuals: The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) targeted sequencing study. PloS One, 2014; 9: e109155
40. Huber M, Lezius S, Reibis R et al: A single nucleotide polymorphism near the CYP17A1 gene is associated with left ventricular mass in hypertensive patients under pharmacotherapy. Int J Mol Sci, 2015; 16: 17456–68
41. Nakajin S, Shively JE, Yuan PM, Hall PF: Microsomal cytochrome P-450 from neonatal pig testis: two enzymatic activities (17 alpha-hydroxylase and c17,20-lyase) associated with one protein. Biochemistry, 1981; 20: 4037–42
42. Gomez-Sanchez CE, Qi X, Velarde-Miranda C et al: Development of monoclonal antibodies against human CYP11B1 and CYP11B2. Mol Cell Endocrinol, 2014; 383: 111–17
43. Biglieri EG, Herron MA, Brust N: 17-hydroxylation deficiency in man. J Clin Invest, 1966; 45: 1946–54
44. Katsumata N, Ogawa E, Fujiwara I, Fujikura K: Novel CYP17A1 mutation in a Japanese patient with combined 17alpha-hydroxylase/17,20-lyase deficiency. Metabolism, 2010; 59: 275–78

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]