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Association of a *CYP4A11* polymorphism and hypertension in the Mongolian and Han populations of China

J.Q. Liang[1,2]*, M.R. Yan[2]*, L. Yang[2], Q. Suyila[2], H.W. Cui[2] and X.L. Su[1,2]

[1]Department of Cell Biology, Capital Medical University, Beijing, China
[2]Clinical Medical Research Center of the Affiliated Hospital,
Inner Mongolia Medical University, Hohhot, Inner Mongolia, China

*These authors contributed equally to this study.
Corresponding author: X.L. Su
E-mail: xlsu2012@gmail.com

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ABSTRACT. Human cytochrome P450 4A11 (CYP4A11) plays a role in the regulation of blood pressure through the conversion of arachidonic acid into 20-hydroxyeicosatetraenoic acid (20-HETE). We therefore investigated the association between a *CYP4A11* polymorphism (rs9333025) with hypertension in the Mongolian and Han ethnic groups. We studied 514 Mongolians in a pastoral area, including 201 hypertension patients and 313 normotensive controls, and 524 Han individuals in an urban area, including 215 hypertension patients and 309 normotensive controls. Genotyping was performed using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). Genotype, allele, and dominant inheritance differed significantly between the Mongolian and Han populations (P = 0.006, P = 0.002, and P = 0.003, respectively). Significant differences were also observed in these factors when considering only males (P = 0.001, P = 0.003, and P = 0.001, respectively). For the Han population, recessive inheritance differed significantly between hypertension

patients and controls and between male patients and controls (P = 0.005 and P = 0.049, respectively). The genotypic, allelic, and dominant frequencies differed significantly between hypertension patients in both populations (P = 0.019, P = 0.035, and P = 0.024, respectively). The genotypic frequency in Mongolian male patients was significantly different from that in Han male patients (P = 0.009). Higher body mass index, triglycerides, and lower high-density lipoprotein were associated with increased risk of developing hypertension in the Han population. The GG genotype was in higher frequency in the Mongolian population, indicating that it is a high risk factor for hypertension. Mongolian men were at higher risk of developing hypertension.

Key words: CYP4A11; Hypertension; Mongolians; Han Chinese

INTRODUCTION

Both genetic and environmental factors contribute to the development of hypertension. Blood pressure is a complex and highly heritable trait with estimates of heritability ranging from 31 to 68% (Ehret, 2010). The candidate gene approach is a valuable tool for identifying common variants of genes involved in the pathogenesis of hypertension. Numerous candidate genes have been investigated for associations with blood pressure and hypertension. However, the etiology and pathogenesis of essential hypertension remain unclear. A number of studies investigating over 15 rare Mendelian hypertensive syndromes have focused on variations in genes involved in renal sodium transport, adrenergic pathways, vascular-related genes and enzymes, and receptors in the aldosterone synthesis or signaling pathways (Basson et al., 2012).

Cytochrome P450 is a superfamily of cysteinato-heme enzymes that catalyze the oxidative transformation of xenobiotics and endogenous molecules. As a member of the cytochrome P450 superfamily, CYP4A11 is mainly involved in catalyzing the conversion of arachidonic acid to 20-hydroxyeicosatetraenoic acid (20-HETE). 20-HETE plays an important role in regulating myogenic contractions of the renal, brain, skeletal muscle, and mesenteric arteries and vascular smooth muscle (Zou et al., 1996; Lasker et al., 2000).

The murine CYP4A14 and CYP4A10 genes are homologs of the human CYP4A11 gene. Mice with knockouts of the CYP4A14 gene (Holla et al., 2001) and the CYP4A10 gene (Nakagawa et al., 2006) showed the hypertensive phenotype. Moreover, the increase in blood pressure levels in male *CYP4A1* (-/-) mice was higher than that in female *CYP4A1* (-/-) mice (Holla et al., 2001). The murine CYP4A14 and CYP4A10 genes have 72.69 and 73.02% amino acid sequence identity to the human CYP4A11 gene, respectively. This relatively higher similarity indicates that the human CYP4A11 gene may have the same function as the murine CYP4A14 and CYP4A10 genes (Nakagawa et al., 2006). The human CYP4A11 gene is located at chromosome 1p33 and contains 12 exons with a length of 12.57 kb. In humans, several *CYP4A11* DNA variants have been reported to be associated with hypertension. The *CYP4A11* T8590C polymorphism (rs1126742), a loss-of-function cytosine (C) to thymidine (T) transition, is associated with hypertension and coronary artery disease in humans (Mayer et al., 2005, 2006; Gainer et al., 2005, 2008; Laffer et al., 2008; Hermann et al., 2009; Williams et al., 2011). Another *CYP4A11* polymorphism, rs9333025, showed a significantly

higher frequency in essential hypertensive Japanese men and was suggested to be a genetic marker for cerebral infarction in Japanese men (Fu et al., 2008a,b). However, no *CYP4A11* polymorphism has yet been investigated in the Chinese Mongolian population. The aim of this study was to determine the association of *CYP4A11* genetic variants with hypertension in the Chinese Mongolian and northern Chinese Han populations. The study populations consisted of Mongolian hypertension patients, Mongolian normotensive individuals (controls), Han hypertension patients, and Han normotensive individuals (controls). This study will provide insights for the identification of hypertension susceptibility genes and other genetic factors in both the Mongolian and northern Chinese Han hypertension population. Furthermore, it will advance our understanding of the pathogenesis of hypertension and provide new ideas for the prevention and treatment of hypertension.

MATERIAL AND METHODS

Study population

The study consisted of 1038 subjects, including 514 Mongolians in a pastoral area and 524 Han Chinese in an urban area. Mongolian subjects were all from families that had been living in the Inner Mongolia Autonomous Region of China for at least three generations. Hypertension patients were diagnosed according to the following World Health Organization (WHO) criteria of 1999: systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or antihypertension treatment. The normotensive controls were selected based on the following criteria: SBP < 140 mmHg and DBP < 90 mmHg and no previous diagnosis of hypertension. The Mongolian population included 201 hypertension patients (92 males and 109 females with an average age of 54.70 ± 10.78 years) with a mean blood pressure of 156 ± 27.80 mmHg/97.15 ± 16.15 mmHg, and 313 normotensive controls (153 males and 160 females with an average age of 44.04 ± 11.48 years) with a mean blood pressure of 119.24 ± 12.92 mmHg/77.65 ± 7.34 mmHg. The Han population consisted of 215 hypertension patients (155 males and 60 females with an average age of 52.21 ± 15.43 years) with a mean blood pressure of 145.86 ± 13.85 mmHg/87.61 ± 11.03 mmHg, and 309 normotensive controls (121 males and 188 females with an average age of 45.83 ± 10.33 years) with a mean blood pressure of 122.33 ± 15.81 mmHg/80.17 ± 10.38 mmHg.

Subjects were invited for a face-to-face interview. The following data were recorded for each subject: name, age, gender, ethnicity, height, weight, history of drinking and tobacco use (smoking was defined as smoking at least one cigarette per day for at least one year, and drinking was defined as consuming 50 g or more alcohol per day for at least one year), and blood pressure. Blood pressure was measured three times for each subject; the SBP and DBP values were calculated as the mean of three measurements. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Blood samples were collected after an overnight fast, and blood glucose, triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were measured within eight hours (Beckman Coulter Unicel DxC 800 Synchron Clinical Systems; Beckman Coulter Company, Fullerton, CA, USA). The clinical characteristics of subjects are listed in Table 1. Informed consent was obtained from all subjects. Our study was approved by the Inner Mongolia Medical University Affiliated Hospital Ethics Committee.

Table 1. Clinical characteristics of patients with essential hypertension and controls in Mongolian and Han population.

Clinical characteristics	Mongolian		u test	P	Han		u test	P	Hypertension		u test	P
	Patients (N = 201)	Controls (N = 313)			Patients (N = 215)	Controls (N = 309)			Mongolian (N = 201)	Han (N = 205)		
Age	54.70 ± 10.78	44.04 ± 11.48	9.461	0.001	52.21 ± 15.43	45.83 ± 10.33	5.63[t]	0.001	54.70 ± 10.78	52.21 ± 15.43	1.909	0.057
Systolic blood pressure	156.24 ± 27.80	119.24 ± 12.92	16.65	0.001	145.86 ± 13.85	122.33 ± 15.81	19.09	0.001	156.24 ± 27.80	145.86 ± 13.85	4.872	0.001
Diastolic blood pressure	97.15 ± 16.51	77.65 ± 7.34	14.77	0.001	87.61 ± 11.03	80.17 ± 10.38	7.897	0.001	97.15 ± 16.51	87.61 ± 11.03	6.999	0.001
Blood glucose	5.58 ± 1.62	5.13 ± 0.52	3.580	0.001	5.38 ± 0.48	5.36 ± 0.57	0.45[t]	0.648	5.583 ± 1.62	5.38 ± 0.48	1.368	0.172
Total cholesterol	4.50 ± 0.89	4.04 ± 0.97	4.791[t]	0.001	4.90 ± 0.88	3.36 ± 1.32	14.88	0.001	4.50 ± 0.89	4.90 ± 0.88	4.687[t]	0.001
Triglycerides	1.49 ± 1.09	0.95 ± 0.53	6.119	0.001	1.95 ± 1.46	2.01 ± 1.30	0.50	0.615	1.493 ± 1.09	1.95 ± 1.46	3.656	0.001
High-density lipoprotein	1.48 ± 0.36	1.55 ± 0.44	1.749[t]	0.081	1.28 ± 0.41	1.33 ± 0.68	0.87	0.381	1.48 ± 0.36	1.28 ± 0.41	5.257	0.001
Low-density lipoprotein	3.44 ± 0.99	2.83 ± 0.98	6.088[t]	0.001	3.03 ± 0.80	2.74 ± 0.81	4.08	0.001	3.44 ± 0.99	3.03 ± 0.80	4.613	0.001
Body mass index	28.87 ± 4.88	24.02 ± 4.15	12.24	0.001	25.11 ± 0.31	24.64 ± 3.48	1.89	0.059	28.87 ± 4.88	25.11 ± 0.31	10.87	0.001
Smoking (No/Yes)[#]	59 (29.35)	98 (31.31)	0.221[b]	0.638	16 (7.44)	20 (6.47)	0.319	0.572	59 (29.35)	16 (7.44)	33.748	0.001
Alcohol consumption (No/Yes)[#]	63 (31.34)	156 (49.84)	15.607	0.001	17 (7.91)	19 (6.15)	0.434	0.612	63 (31.34)	17 (7.91)	36.735	0.001

[b]Fisher's exact test. [t]*t*-test. [#]χ^2 test. We used the u test for the other data which were not marked.

DNA extraction and *CYP4A11* polymorphisms analysis

Genomic DNA was isolated from 1 mL blood samples using the BloodGen Mini Kit (CWBIO, China). The single nucleotide polymorphism (SNP) was genotyped by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). PCR primers were purchased from TaKaRa Biotechnology (Dalian, China). PCR was performed using the following primers: forward, 5'-CAC TGA GTG GCG TGT TGA G-3' and reverse, 5'-TGC CTG GAC TGT ATG GTT TT-3'. Amplification was performed under the following conditions: initial denaturation of 2 min at 94°C followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 59.8°C for 30 s, and extension at 72°C for 1 min, followed by a final extension at 72°C for 7 min. PCR products were digested with *Hin*fI (NEB, Beijing, China) at 37°C for 4 h and stored at 4°C. Restriction DNA fragments were separated by electrophoresis on 4% agarose gel and stained with ethidium bromide. The gel was then visualized under UV illumination.

Sequencing

To confirm the results of the PCR-RFLP analysis, we performed sequencing on randomly selected samples. DNA sequences were verified by direct sequencing (ABI Prism 3700 DNA analyzer 377; Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) of the *CYP4A11* genotype distributions in the study populations was evaluated with the chi-squared test. Allelic and genotypic frequencies between groups were analyzed using the chi-squared test. The risk factors for hypertension were assessed using logistic regression analysis. The Student *t*-test and the Mann-Whitney *U*-test were used to compare clinical characteristics. All analyses were performed using the SPSS13.0 software. A two-tailed P value < 0.05 was considered to be statistically significant.

RESULTS

The National Centre for Biotechnology Information (NCBI) SNP database contains more than 120 SNPs for the human *CYP4A11* gene. The SNP RS9333025 was selected herein owing to its relatively high association with hypertension in a previous study (Fu et al., 2008a). The association between this polymorphism with hypertension was investigated among the hypertension patients and controls in both the Mongolian and Han populations.

After amplification and digestion of *CYP4A11*, the following restriction fragments were expected for this polymorphism: 253 and 139 bp for the homozygous wild-type (AA genotype), 392 bp for the homozygous mutant (GG genotype), and 392, 253, and 139 bp for the heterozygote (GA genotype) (Figure 1).

We observed that the *CYP4A11* polymorphism genotype distribution was in accordance with HWE in the studied population ($P > 0.05$). There were significant differences in genotype, allele, and dominance between the Mongolian and Han populations ($P = 0.006$, $P = 0.002$, and $P = 0.003$, respectively; Table 2). Significant differences of genotype, allele, and dominance were also observed in males between these two populations ($P = 0.001$, $P = 0.003$, and $P = 0.001$,

respectively; Table 2). For the Mongolian population, the distributions of genotypic and allelic frequencies of the *CYP4A11* polymorphism were similar in the hypertension patients and controls, with a higher GG genotypic frequency in both groups. The genotypic and allelic frequencies of the *CYP4A11* polymorphism were not significantly different between hypertensive patients and controls for all the subjects or in either gender (Table 3). For the Han population, a significant difference in recessive inheritance was found between hypertension patients and controls and between male patients and controls (P = 0.005 and P = 0.049, respectively; Table 4). Significant differences were observed for the genotypic, allelic, and dominant frequencies of the *CYP4A11* polymorphism between hypertension patients in the Mongolian and Han populations (P = 0.019, P = 0.035, and P = 0.024, respectively; Table 5). The genotypic frequency of this variant in Mongolian male patients was significantly different from that in Han male patients (P = 0.009, Table 5).

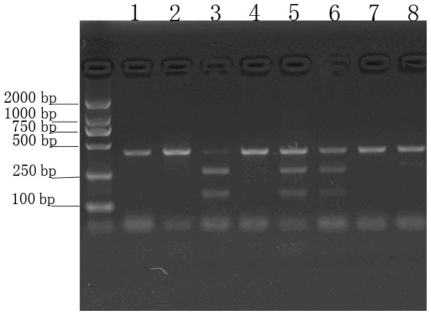

Figure 1. Agarose gel electrophoresis of PCR-RFLP products of CYP4A11 polymorphisms. *Lane M* = marker. *Lane 3* = homozygous wild-type (AA); *lanes 1*, *2*, *4*, *7*, and *8* = mutant homozygote (GG); *lanes 5* and *6* = heterozygote (AG).

Table 2. Genotype and allele distributions of CYP4A11 polymorphism in Mongolian and Han population.

		All		P	Male		P	Female		P
		Mongolian	Han		Mongolian	Han		Mongolian	Han	
Genotype	GG	382 (74.31)	342 (65.27)	0.006	190 (77.55)	175 (63.40)	0.001	192 (71.37)	167 (67.33)	0.411
	GA	118 (22.95)	165 (31.48)		48 (19.59)	95 (34.42)		70 (26.02)	70 (2.82)	
	AA	14 (2.72)	17 (3.24)		7 (2.85)	6 (2.24)		7 (2.60)	11 (4.43)	
Dominance	GG	382 (74.31)	342 (65.27)	0.002	190 (77.55)	175 (63.40)	0.001	192 (71.37)	167 (67.33)	0.320
	GA+AA	132 (25.68)	182 (34.730)		55 (25.70)	101 (36.60)		77 (28.63)	81 (32.37)	
Recessive	AA	14 (2.72)	17 (3.24)	0.622	7 (2.85)	6 (2.24)	0.618	7 (2.61)	11 (4.44)	0.265
	GG+AG	500 (97.27)	507 (96.75)		238 (97.14)	270 (97.82)		262 (97.39)	237 (95.56)	
Allele	G	882 (85.79)	849 (81.01)	0.003	428 (87.34)	445 (80.61)	0.003	454 (84.38)	408 (81.60)	0.232
	A	146 (14.21)	199 (18.98)		62 (12.66)	107 (19.39)		84 (15.62)	92 (18.40)	

Table 3. Genotype and allele distributions of CYP4A11 polymorphism in patients with essential hypertension and in controls for Mongolian population.

		All mongolians		P	Mongolian male		P	Mongolian female		P
		Patients	Controls		Patients	Controls		Patients	Controls	
Genotype	GG	153 (76.12)	229 (73.16)	0.658	71 (76.08)	119 (77.77)	0.958	82 (75.23)	110 (68.75)	0.466
	GA	42 (21.00)	76 (24.28)		18 (19.56)	30 (19.60)		24 (22.02)	46 (28.75)	
	AA	6 (2.98)	8 (2.56)		3 (3.26)	4 (2.61)		3 (2.75)	4 (2.50)	
Dominance	GG	153 (76.12)	229 (73.16)	0.454	71 (76.08)	119 (77.77)	0.913	82 (75.23)	110 (68.75)	0.160
	GA+AA	48 (23.88)	84 (26.84)		21 (23.92)	34 (22.23)		25 (24.77)	50 (31.25)	
Recessive	AA	6 (2.98)	8 (2.56)	0.771	3 (3.26)	4 (2.61)	0.630	3 (2.75)	4 (2.50)	0.918
	GG+AG	195 (97.51)	305 (97.44)		77 (96.7.4)	149 (97.38)		108 (99.08)	156 (97.50)	
Allele	G	348 (86.57)	534 (85.30)	0.574	160 (85.56)	268 (87.58)	0.520	188 (86.24)	266 (83.13)	0.329
	A	54 (13.43)	92 (14.69)		27 (14.44)	38 (12.42)		30 (13.76)	54 (16.87)	

Table 4. Genotype and allele distributions of CYP4A11 polymorphism in patients with essential hypertension and in controls for Han population.

		All Han individuals		P	Han male		P	Han female		P
		Controls	Patients		Controls	Patients		Controls	Patients	
Genotype	GG	200 (64.72)	142 (66.05)	0.135	77 (63.63)	98 (63.23)	0.129	123 (65.42)	44 (73.33)	0.519
	GA	95 (30.74)	70 (32.56)		39 (32.23)	56 (36.13)		56 (29.78)	14 (23.33)	
	AA	14 (4.53)	3 (1.39)		5 (4.13)	1 (0.65)		9 (4.78)	2 (3.33)	
Dominance	GG	200 (64.72)	142 (66.05)	0.755	77 (63.63)	98 (63.23)	0.944	123 (65.42)	44 (73.33)	0.160
	GA+AA	109 (35.27)	73 (33.95)		44 (36.36)	57 (36.77)		27 (34.57)	16 (26.67)	
Recessive	AA	14 (4.53)	3 (1.39)	0.005	5 (4.13)	1 (0.65)	0.049	9 (4.78)	2 (3.33)	0.634
	GG+AG	195 (95.46)	212 (98.60)		116 (95.86)	154 (99.35)		179 (95.21)	58 (96.67)	
Allele	G	495 (80.09)	354 (81.76)	0.502	193 (79.75)	252 (81.03)	0.707	302 (80.31)	102 (85.00)	0.251
	A	123 (19.9)	79 (18.24)		49 (20.24)	59 (18.97)		74 (19.68)	18 (15.00)	

Table 5. Genotype and allele distributions of CYP4A11 polymorphism in patients with essential hypertension for Mongolian and Han population.

		All patients		P	Male patients		P	Female patients		P
		Mongolian	Han		Mongolian	Han		Mongolian	Han	
Genotype	GG	153 (76.12)	142 (66.05)	0.019	71 (76.08)	98 (63.23)	0.009	82 (75.23)	44 (73.33)	0.955
	GA	42 (21.00)	70 (32.56)		18 (19.56)	56 (36.13)		24 (22.02)	14 (23.33)	
	AA	6 (2.98)	3 (1.39)		3 (3.26)	1 (0.65)		3 (2.75)	2 (3.33)	
Dominance	GG	153 (76.12)	142 (66.05)	0.024	71 (76.08)	98 (63.23)	0.023	82 (75.23)	44 (73.33)	0.787
	GA+AA	48 (23.88)	73 (33.95)		21 (23.92)	57 (36.77)		27 (24.77)	16 (26.67)	
Recessive	AA	6 (2.98)	3 (1.39)	0.265	3 (3.26)	1 (0.65)	0.081	3 (2.75)	2 (3.33)	0.977
	GG+AG	195 (97.51)	212 (98.60)		77 (96.7.4)	154 (99.35)		106 (99.08)	58 (96.67)	
Allele	G	348 (86.57)	354 (81.76)	0.035	160 (85.56)	252 (81.03)	0.195	188 (86.24)	102 (85.00)	0.755
	A	54 (13.43)	79 (18.24)		27 (14.44)	59 (18.97)		30 (13.76)	18 (15.00)	

Logistic regression analysis showed that hypertension risk factors (BMI, TG, HDL, age, and alcohol consumption) had significant effects only in the Han population (Table 6).

Table 6. Logistic regression analysis for the risk factors of hypertension in Mongolian and Han population.

Risk factor	Mongolian			Han		
	OR	95%CI	P	OR	95%CI	P
Age	0.785	0.391-1.575	0.496	0.387	0.222-0.675	0.010
Male/female	0.878	0.405-1.905	0.743	1.285	0.589-2.805	0.528
Body mass index	1.409	0.455-4.365	0.552	2.133	0.999-4.557	0.050
Blood glucose	0.816	0.229-2.909	0.754	0.821	0.165-4.088	0.810
Cholesterol	1.253	0.405-3.872	0.696	0.885	0.330-2.374	0.809
Triglycerides	1.142	0.441-2.959	0.785	2.290	1.127-5.676	0.047
High-density lipoprotein	0.160	0.020-1.297	0.086	2.355	1.009-5.497	0.048
Low-density lipoprotein	0.440	0.164-1.181	0.103	1.168	0.454-3.009	0.747
Systolic blood pressure	1.109	0.438-2.809	0.827	1.790	0.778-4.117	0.171
Diastolic blood pressure	0.785	0.322-1.909	0.593	0.536	0.262-1.097	0.088
Smoking (No/Yes)	0.972	0.457-2.067	0.940	0.212	0.028-1.600	0.133
Alcohol consumption (No/Yes)	0.845	0.357-1.999	0.702	0.131	0.021-0.795	0.027

No genotyping discrepancies were found between PCR-RFLP and direct sequencing of the PCR products. The GA genotype from PCR-RFLP was confirmed by the double peaks at position 215 in the sequence (indicated by the arrow in Figure 2A). The GG and AA genotypes were confirmed by a single peak (indicated by arrows in Figure 2B, C).

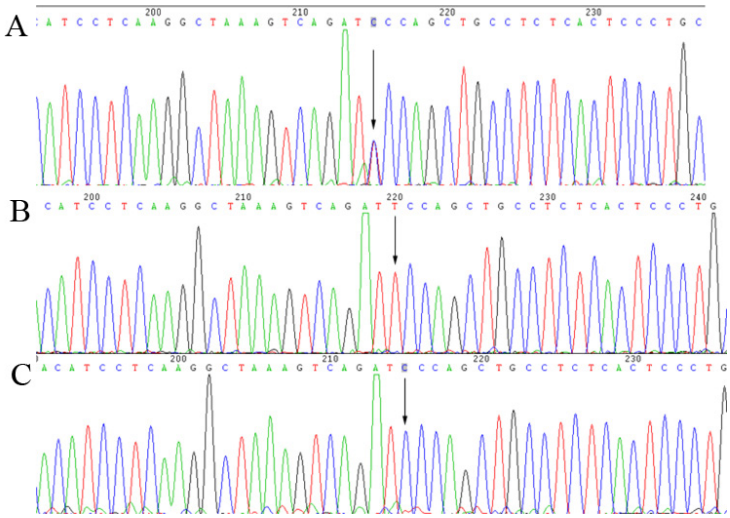

Figure 2. Sequencing of the PCR product. The results of direct sequencing of PCR products showed GA (**A**), AA (**B**), and GG (**C**) genotypes. All the results were reverse sequencing.

DISCUSSION

Multiple studies have reported genes involved in essential hypertension, both in monogenic and polygenic forms. The occurrence of essential hypertension is attributed to genetic, environmental factors, and the interaction of genes. Essential hypertension is a disorder that results from the inheritance of a number of susceptibility genes (Imaoka et al., 1993; Andersen et al., 2005). Therefore, genetic factors play an important role in the pathogenesis of hypertension.

The cDNA-deduced amino acid sequence of human CYP4A11 was first determined by Imaoka and colleagues in 1993 (Imaoka et al., 1993). The CYP4A11 gene is located at chromosome 1p33, encodes a protein of 519 amino acids, and contains 12 exons and 11 introns. *CYP4A22* (AF208532) is homologous to the *CYP4A11* gene sharing 96% of overall nucleotide sequence identity (Bellamine et al., 2003). An SNP (g.4628G>A, p.Gly130Ser) was identified in *CYP4A22* exon 3, which confers an amino acid change from glycine to serine (Cardenas et al., 2011), resulting in a non-functional protein (Gainer et al., 2005).

It was reported that several *CYP4A11* polymorphisms are associated with cardiovascular and cerebrovascular diseases. The *CYP4A11* T8590C polymorphism, a loss-of-function mutation, has been widely studied. The *CYP4A11* 8590C allele is associated with increased blood pressure (Mayer et al., 2006; Gainer et al., 2008) and hypertension (Gainer et al., 2005; Mayer et al., 2005; Fu et al., 2008a; Williams et al., 2011), and showed impacts on coronary endothelial function (Hermann et al., 2009). A novel polymorphism of *CYP4A11* (rs3890011) was found to be associated with coronary artery disease in the Han Chinese population (Fu et al., 2013a,b). The *CYP4A11* polymorphism rs9333025 was associated with essential hypertension and cerebral infarction in Japanese men (Fu et al., 2008a,b). A haplotype-based study of *CYP4A11* was performed in the Japanese and Chinese populations. The G-G-T (rs9332978, rs3890011, rs1126742) haplotype in coronary artery disease was significantly higher than that

in the control group in the Han Chinese population (Fu et al., 2013b). The frequency of the T-T-A haplotype (rs2269231, rs1126742, rs9333025) was significantly lower in myocardial infarction patients than in control subjects in the Japanese population (Fu et al., 2012). The T-C-G haplotype (rs2269231, rs1126742, rs9333025) was significantly more frequent in control subjects than in cerebral infarction patients in the Japanese population (Fu et al., 2008b). The A-T-G haplotype frequency (rs2269231, rs1126742, rs9333025) was significantly higher in essential hypertension men than in control men in the Japanese population (Fu et al., 2008a). Our results found significant differences in genotype, allele, and dominance between the Mongolian and Han populations (P = 0.006, P = 0.002, and P = 0.003, respectively). A significant difference was observed in recessive inheritance between Han hypertension patients and controls (P = 0.005). The genotypic, allelic, and dominant frequencies of the *CYP4A11* polymorphism in Mongolian patients were significantly different from those in Han patients (P = 0.019, P = 0.035, and P = 0.024, respectively). These results suggest that the *CYP4A11* GG genotype was a high risk factor for hypertension.

A gender difference exists in the occurrence of hypertension. Mice with knock-outs of the *CYP4A14* gene (Holla et al., 2001) and the CYP4A10 gene (Nakagawa et al., 2006) showed the hypertensive phenotype. Moreover, blood pressure in male *CYP4A1* (-/-) mice was higher than that of female *CYP4A1* (-/-) mice (Holla et al., 2001). Therefore, the subjects herein were analyzed with respect to 3 categories: all subjects, male subjects only, and female subjects only. There were significant differences in genotype, allele, and dominance between the male Mongolian and Han populations (P = 0.001, P = 0.003, and P = 0.001, respectively). A significant difference in recessive inheritance was found between male Han patients and controls (P = 0.049). The genotypic frequency of this variant in the Mongolian male patient group was significantly different from that in the Han male patient group (P = 0.009). These results suggest that men, and especially Mongolian men, are at higher risk for developing hypertension. Higher BMI, higher TG levels, and lower HDL levels were associated with increased risk of developing hypertension in the Han population. Further study is needed to investigate the effect of the *CYP4A11* gene mutation on blood pressure, and the relationship between its functional change and hormone metabolism. This will help to better elucidate the mechanism of hypertension development and advance our understanding of the genetic aspects of hypertension.

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