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Angiotensinogen M235T, β2 Adrenergic Receptor Arg16Gly and Aldosterone Synthase C-344T Gene Polymorphisms and Essential Hypertension among Han Population Living at High Altitude in China

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Abstract

We explored the association of angiotensinogen (AGT) M235T, β2 adrenergic receptor (β2-AR) Arg16Gly and aldosterone synthase (CYP11B2) C-344T genes polymorphisms with essential hypertension (EH) in Han population living at high altitude in China. A total of 390 hypertensive subjects (males, 207; females, 183) and 424 normal healthy individuals (males, 251; females, 173) were enrolled in this study based on the inclusion and exclusion criteria. The polymorphisms of AGT M235T, β2-AR Arg16Gly, CYP11B2 C-344T genes were analyzed by Snapshot mini sequencing method. The frequencies of CC genotype and C allele of AGT M235T in EH group were higher than in control ($p<0.05$), gender wise analysis revealed that the genotype and allele patterns between patients and controls were found to be significantly different ($p<0.05$). However, genotype and allele frequencies of the distribution of β2-AR Arg16Gly and CYP11B2 C-344T between EH patients and normotensive controls were not significantly different ($p>0.05$, respectively), in gender-specific analysis, the differences were also not found ($p>0.05$, respectively). This finding suggests that the polymorphism of AGT M235T was correlated with EH in Han population living at high altitude in China, however, β2-AR Arg16Gly and CYP11B2 C-344T polymorphism were unlikely to associated with hypertensive subjects of this population.

Keywords: AGT M235T; β2-AR Arg16Gly; CYP11B2 C-344T; Polymorphism; Essential hypertension; Han population

Introduction

Essential hypertension (EH) is one of the most common diseases of human being, and also is an important cause for the myocardial infarction, cerebral apoplexy, and some serious nephropathy etc. which is a complex multifactorial condition influenced by both genetic and environmental factors [1]. Epidemiological and family based studies in many geographically and ethnically distinct populations indicate that EH is a multifactorial disorder with a familial tendency, while it is influenced by race, gender, diet and so on [2]. As there is a complex interaction between a variety of genetic and environmental factors in EH, the precise cause has not been determined [3]. Renin angiotensin (RA) system is a powerful regulatory system with an effective influence on salt and water metabolism and blood pressure (BP). AGT is the precursor protein to angiotensin II, which plays a primary role in the regulation of BP by the RA system. The M235T mutation of AGT gene is a single base pair substitution of thymine with cytosine at nucleotide 704 (T704C) in exon 2 of the AGT gene. It is known that due to M235T polymorphism, the level of circulating angiotensinogen is increased and the individuals are hypertensive [4,5].

The sympathetic nervous system plays a major role in BP regulation. β2-AR have a pivotal role in the sympathetic nervous system, it is a G-protein coupled receptor that, upon activation by catecholamine, increases the intracellular second messenger cyclic adenosine monophosphate (cAMP) [6]. β2-AR Gly16Arg polymorphism is localized in the extracellular amino terminus region of the protein, which has been characterized that arginine substituted by glycine at nucleotide 16 [7]. Studies have demonstrated that the Gly16Arg genotypes appear to influence the degree of agonist induced receptor desensitization, the functional importance of the Arg16Gly polymorphism has been studied in mediating the vasodilatation that is important in blood pressure control. Other blood pressure regulating effects of the β2 adrenoceptor include renal sodium handling and control of renin release [8-10].

CYP11B2 gene encodes for a cytochrome P450 enzyme, involved in the terminal steps of aldosterone synthesis, aldosterone acts on the distal nephron to regulate sodium resorption, potassium excretion, an intravascular volume [11]. Aldosterone levels are also associated with polymorphic variation in the CYP11B2 gene, the C-344T polymorphism have been identified to be mediate sodium balance and arterial pressure by influencing intravascular volume and arterial thickness which associated with EH in different population groups [12-14].

The associations between the genetic variations in these genes and hypertension would thus be of significant interest. However, to date, associations with these variants are found to be contradictory in different populations. Gannan district of Gasu province is located in the northeastern margin of the Qinghai-Tibet Plateau of China; the average altitude of this area is about 3,500 m above sea. In this study, we aim to investigate the AGT M235T, β2-AR Arg16Gly and CYP11B2 C-344T genes polymorphism in EH patients and healthy controls among Han populations who resided in this area by using Snapshot

minisequencing method, through comparing the genotype and allele frequencies, to assess whether the polymorphism of above genes are associated with genetic predisposition to EH.

Materials and Methods

Subjects

A total of 814 participants aged 18 to 70 years old who resided in Gansu province were randomly selected and completed the survey. The subjects were divided into hypertensive (patients) and normotensive (controls) individuals. The survey was conducted in May to September of 2014, we used ways of concentrated investigation and household visits, informed consent were obtained from each patient.

The first measurement of BP after 5 min time of rest was taken on the right arm of each participant who is in a seated position, and then research team performed three successive measurements with at least a 1 min time interval between measurements. The average of the three measurements of BP was used for analysis. A standardized mercury sphygmomanometer was used. Patients were diagnosed in accordance with JNC 7 guidelines and hypertension was defined as systolic BP (SBP) ≥ 140 mm Hg and/or diastolic BP (DBP) ≥ 90 mm Hg, and/or self-reported treatment of hypertension with anti-hypertension medication taken in the past 2 weeks. The exclusion criteria were individuals with secondary hypertension (due to renovascular disease, renal failure, pheochromocytoma, aldosteronism or other causes of secondary hypertension). The normotensive subjects who had BP <140/90 mm Hg, no history of cardiovascular, no positive familial history of EH, no diabetes mellitus or other systemic diseases were considered as controls. All the individuals in the control group had never been treated with antihypertensive medication. In this case-control study, a total of 390 EH subjects and 424 controls were enrolled.

Genotype determination

The blood samples were taken into EDTA-containing containers and stored in -20°C, genomic DNA was extracted using a DNA extraction kit (Sangon Biotech Shanghai, China) based on the manufacturer's protocol, and stored at -70°C. The AGT M235T, β2-AR Arg16Gly and CYP11B2 C-344T genes polymorphism was determined by SnaPshot minisequencing. The primers of three genes used were as Table 1.

Gene	SNP	Primer	Fragments
AGT	M235T	Forward CTTGGGGAGCTGAAGGACTACTAC	273 bp
		Reverse CACTTTGTGACCATTCCGGTTTG	
β2-AR	Arg16Gly	Forward ATGAGGCTTCCAGGCGTC	230 bp
		Reverse GATGAGAGACATGCGATGCC	
CYP11B2	C-344T	Forward CAGGGCTGAGAGGAGTAAAA	295 bp
		Reverse CAGGGGGTACGTGGACATTT	

Table 1: The primers and reaction fragments of AGT M235T β2-AR Arg16Gly and CYP11B2 C-344T.

PCR amplification were performed in 20 μl final volume, with 2.0 μl buffer, 0.5 μl of dNTPs, 0.8 μl of $MgCl_2$, 0.2 μl of Platinum Taq (5U), 1.0 μl of primer, 1.0 μl of genomic DNA and 14.5 μl of ddH_2O.The cycling conditions included initial denaturation for 2 min at 95°C, followed by 35 cycles of denaturation at 95°C for 30s, annealing at 58°C for 30s, extension at 72°C for 30 s and final extension for 5 min at 72°C. 2.0 μL of the PCR product was cleaned up with 0.2 μL of ExoI, 0.3 μL of Shrimp Alkaline Phosphatase (SAP) (1U/ul) (Sangon Biotech Shanghai, China) and 7.5 μl of ddH_2O, incubated at 37°C for 100 min followed by 75°C for 15 min to inactivate the enzyme, and stored at 4°C for 24 hours. Single Base Extensions were performed in a total volume of 5.0 μL comprising 2.5 μL of Reaction mix (Sangon Biotech Shanghai, China), 1.5 μL of cleaned PCR product, 0.7 μL of probe mix and 0.3 μL of GC buffer. The cycling conditions were 96°C for 10 s, 51°C for 5 s and 60°C for 30 s, for 25 cycles. 5.0 μL of the extension product was cleaned up with 0.5 μL of SAP and 2.5 μl of ddH_2O, incubated at 37°C for 1 h, and at 75°C for 15 min to inactivate the enzyme. 1.0 μL of the purified minisequencing products was mixed with 8.5 μL of deionized formamide and 0.5 μL of GeneScan-120 LIZ size standard (Applied Biosystems, USA), and then samples were denatured at 95°C for 5 min. The electrophoresis was run on an ABI 3730 Genetic Analyzer (Applied Biosystems, USA). The data was collected using 3730 Genetic Analyzer Data Collection Software and then analyzed with GeneMapper ID Software v3.2 (Applied Biosystems, USA).

Statistical Analysis

The statistical software package SPSS18.0 (Version 18.0; SPSS, Chicago) was used. Categorical variables were expressed as proportions (%) and continuous variables as mean ± standard deviation. All comparisons between EH group and the control group for continuous variables were performed by independent t-test, and comparisons among genotypic groups were analyzed with one way ANOVA. The chi square test was performed to compare genotype/allele frequency, $P<0.05$ was considered statistically significant.

Results

Characteristics of subjects

All the individuals belonged to the general population, baseline clinical characteristics of subjects enrolled (Table 2). The age and sex matched individuals were included in the study, the SBP, DBP and BMI were higher among the patients as compared to controls ($p<0.05$).

Group	N	Male/Female	Age (years)	BMI (kg/m^2)	SBP (mm Hg)	DBP (mm Hg)
EH	390	207/183	46.6 ± 9.7	23.3 ± 2.6*	155.8 ± 13.3*	100.6 ± 8.8*
NT	424	251/173	48.0 ± 10.6	21.0 ± 1.5	124.2 ± 14.1	83.4 ± 7.2

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; *P<0.05

Table 2: Baseline characteristics of subjects.

Results of PCR products and SnaPshot minisequencing

The PCR products (Figure 1), a typical SNaPshot minisequencing of samples (Figure 2). The different color of product peaks denoted different alleles SNP locus, and the fragment size of alleles among different SNP loci was different.

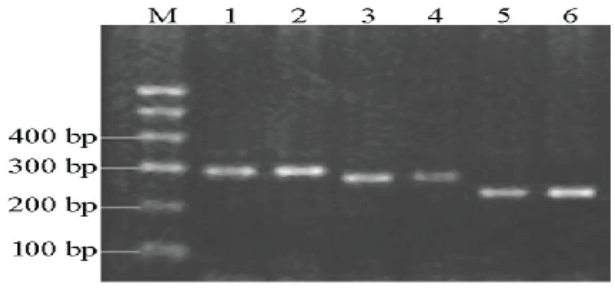

Figure 1: The PCR products.

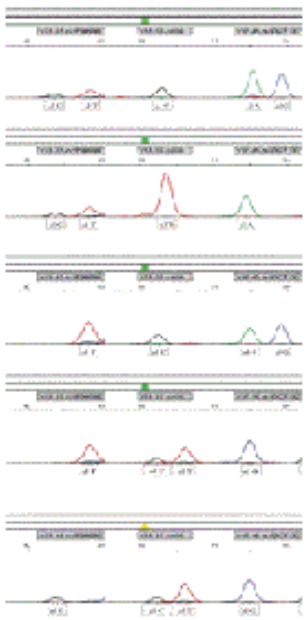

Figure 2: A typical SNaPshot minisequencing of samples.

Analysis of the genotypes and alleles

A total of 798 venous blood samples were collected from the subjects 722 in AGT M235T, 708 in β2- AR Arg16Gly and 701 in CYP11B2 C-344T in study were successfully analyzed, respectively. The analysis of the genotypes and alleles (Table 3).

Gene/SNP	Genotype/ Allele	No. (frequency%)		χ2	p
		EH	NT		
AGT /M235T	CC	260 (74.9)	254 (67.7)	8.20	0.01
	CT	72 (20.7)	92 (24.5)		
	TT	15 (4.3)	29 (7.7)		
	C	592 (85.3)	600 (80.0)	5.47	0.02
	T	102 (14.7)	150 (20.0)		
β2-AR /Arg16Gly	AA	105 (30.9)	109 (29.6)	0.57	0.75
	AG	181 (53.2)	200 (54.3)		
	GG	54 (15.9)	59 (16.0)		
	A	391 (57.5)	418 (56.8)	0.62	0.46
	G	289 (42.5)	318 (43.2)		
CYP11B2 /C344T	CC	44 (13.0)	43 (11.9)	2.02	0.38
	CT	143 (42.3)	149 (41.0)		
	TT	151 (44.7)	171 (47.1)		
	C	231 (34.2)	235 (32.4)	1.15	0.30
	T	445 (65.8)	491 (67.6)		

Table 3: Genotype and allele frequencies of AGT M235T, β2-AR Arg16Gly and CYP11B2 C-344T polymorphism in EH and control group.

It can been found that the CC genotype and C allele of AGT M235T were higher in the EH group compared to control group ($p<0.05$), in gender-wise analysis of the AGT M235T polymorphism revealed that the genotype and allele patterns between patients and controls groups were found to be significantly different both in male and female populations ($p<0.05$) (Table 4). However, the frequencies of genotype and allele were not significant difference between EH group and control group in β2-AR Arg16Gly and CYP11B2 C-344T polymorphisms analysis ($p>0.05$), on gender wise analysis, the differences were also not found ($p>0.05$).

Gene/SNP	Genotype/Allele	No. (frequency%)							
		Male				Female			
		EH	NT	χ2	p	EH	NT	χ2	p
AGT/M235T	CC	140 (75.3)	149 (67.1)	7.79	0.01	120 (74.5)	105 (68.6)	5.36	0.02
	CT	38 (20.4)	55 (24.8)			34 (21.1)	37 (24.2)		
	TT	8 (4.3)	18 (8.1)			7 (4.3)	11 (7.2)		
	C	318 (85.5)	353 (79.5)	4.68	0.03	274 (85.1)	247 (80.7)	4.73	0.03
	T	54 (14.5)	91 (20.5)			48 (14.9)	59 (19.3)		
β2-AR /Arg16Gly	AA	56 (30.4)	67 (29.5)	2.16	0.34	49 (31.4)	42 (29.8)	1.29	0.25
	AG	97 (52.7)	123 (54.2)			84 (53.8)	77 (54.6)		
	GG	31 (16.8)	37 (16.3)			23 (14.7)	22 (15.6)		
	A	209 (56.8)	257 (56.6)	0.06	0.8	182 (58.3)	161 (57.1)	0.16	0.68
	G	159 (43.2)	197 (43.4)			130 (41.7)	121 (42.9)		
CYP11B2/C-344T	CC	23 (12.7)	26 (11.8)	0.63	0.72	21 (13.4)	17 (11.9)	1.6	0.21
	CT	76 (42.0)	90 (40.9)			67 (42.7)	59 (41.3)		
	TT	82 (45.3)	104 (47.3)			69 (43.9)	67 (46.8)		
	C	122 (33.7)	142 (32.3)	0.09	0.75	109 (34.7)	93 (32.5)	2.11	0.34
	T	240 (66.3)	298 (67.7)			205 (65.3)	193 (67.5)		

Table 4: Gender wise comparison of genotype and allele frequencies of AGT M235, β2-AR Arg16Gly and CYP11B2 C-344T polymorphism in EH and control group.

Discussion

EH is a polygenic disorder. It is widely accepted that EH subjects appear to have inherited an aggregate of genes related to hypertension and/or to have been exposed to exogenous factors that predispose them to hypertension. Epidemiological studies suggested that genetics accounts for 30 to 40% of BP changes, studies on candidate gene polymorphisms and their association with EH can help take up proper interventional/treatment strategies [15]. Genes of AGT, β2-AR and CYP11B2 are natural candidates for BP regulation which have been observed in various previous studies. The association between the polymorphism of AGT M235T, β2-AR Arg16Gly and CYP11B2 C-344T and hypertension has been investigated by many researchers, some evidences of association between these genes had been reported but on the contrary these associations were not always significant [4-6,8-10,12-14]. The variety in these results could be due to differences in ethnicity. Han is the largest nationality in China, hypertension has been studied extensively in this population, but most studies were drawn from subjects in low altitude. Because of the remoteness, continuous mountains, and difficult weather conditions in the region residents inhabit, and little is known about the genetic background, the studies between hypertension and genes polymorphism in high altitude areas are scarce. Therefore, we chose this population to study and expect to know the association of polymorphisms about these three genes and their relationship with EH.

The potential role of the molecular variants M235T of AGT gene in hypertension was originally explored by Jeunemaitre group through linkage and association study in the causation of human EH in Utah and French populations [16]. A series of studies among the UK, Malaysian, and south Indian supported the former finding [17-19], several meta- analyses concluded that the coding polymorphism of AGT M235T was associated with increased risk of hypertension [6,20]. However, subsequent association studies found a negative association in Japanese, Germany, African-Americans and North India [21-23]. In China, Cai et al. have found that a significantly higher frequency of the C allele was observed in EH patients when compared to the control subjects among Han population lived in south of China [24]. The distribution of M235T genotypes and alleles in this study were similar to that found in population who reside in south of China. Recent findings revealed that G-6A polymorphism, which is linked to nonfunctioning M235T, increased the plasma AGT level via regulation of AGT gene transcription, and was involved in the pathogenesis of the predisposition to EH [16]. It was also supposed that sex hormones might bind to the core promoter region and enhance the transcription of AGT gene [25]. In gender-wise analysis of our study revealed that the genotype and allele patterns between patients and controls groups were found to be significantly different both in males and females.

The β2-AR is a G protein-coupled receptor that increase intracellular cAMP of the vascular smooth muscle, resulting in vasodilatation, which in turn lowers the peripheral resistance and hence lowers BP [26]. Other effects include renal sodium handling and

control of renin release. Numerous studies have attempted to determine the association of the β2-AR variants with hypertension and related conditions. The relation -ships between the polymorphisms of the β2-AR gene and cardiovascular phenotypes have been assessed in different populations, but the results were lack of an apparent consistency [27-29]. The β2-AR gene locus has been linked both to systolic and diastolic BP in large populations studies in United States [30], similar association was also found in Chinese and in Caribbean populations [28,31]. In vitro studies demonstrated that the Gly16 variant showed enhanced agonist-promoted down regulation [32]. Masuo et al. demonstrated that individuals with Gly16 alleles showed higher BP and plasma norepinephrine than Arg16 carriers in a cohort study [33]. In contrast, there was no association between β2-AR variants and BP in Japanese and black African populations [34,35]. The negative association between the Gly16Arg and EH in our study was similar to the later, further analysis were also not found significant evidence in gender- wise analysis.

Aldosterone plays an important role in BP homeostasis, CYP11B2 gene encodes aldosterone synthase and the polymorphic variation is associated with aldosterone levels [36]. The position of the C-344T polymorphism of CYP11B2 gene is located in the promoter region. Studies revealed that the C-344T polymorphism at the SF-1 site is thought to alter the sensitivity of aldosterone synthase to angiotensin II [37]. The persons with C allele might have the higher efficiency of angiotensin II synthesis, which resulted in the more aldosterone synthase that could increase BP [38]. There were some studies showing the C allele of this gene polymorphism is associated with genetic predisposition to hypertension, some are associated with the T allele, and others are not associated [39-43]. In our study, no association was found both in normotensive controls and EH patients, gender-wise analysis was also not found. However in our study among females of Tibetan resided in this region, the frequency of CC genotype and C allele in the EH group was significantly higher than the normotensive controls. The difference might be attributed to different genetic background.

High altitude has long been considered a cause of hypertension, but Steven, et al, reported that altitude and climate were not important factors contributing to prevalence of hypertension [44]. Sun et al., revealed no significant correlation with altitude and the age-standardized prevalence of hypertension [45]. But the exactly relationship between them is still not entirely clear.

SnaPshot minisequencing technique is based on the high accuracy of nucleotide incorporation by DNA polymerases. Because of the accuracy, rapidity and reliability of this method, we studied the relationship between the polymorphism of AGT M235T、β2-AR Arg16Gly and CYP11B2 C-344T and EH in this population. Differences in population or in experimental conditions may have influenced the discrepancy in the results, other potentially confounding factors such as the different background characteristics of the subjects, genetics epitasis and the influence of environmental factors may be attributed to the discrepancy.

To our knowledge, this is the first study conducted in Han population, living at high altitude in China, which reported the relationship between polymorphism of AGT M235T、β2-AR Arg16Gly and CYP11B2 C-344T and EH. In conclusion, it was found that AGT M235T polymorphism may be a predisposing factor in the development of EH in Han population resided in this area. There were no associations can be observed between polymorphism of β2-AR Arg16Gly and CYP11B2 C-344T and EH in this population.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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