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Original Article

Relationship between M235T and T174M polymorphisms in angiotensin gene and atrial fibrillation in Uyghur and Han populations of Xinjiang, China

Bannu Kuken[1,2], Yuchun Yang[2], Zhiqiang Liu[2], Pengyi He[2], Muhuyati Wulasihan[2]

[1]Department of Cardiology, The Second Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region, China; [2]Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region, China

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Abstract: Objective: To elucidate the association between angiotensin gene (AGT) M235T and T174M genetic polymorphisms in Han and Uyghur patients with atrial fibrillation (AF) in Xinjiang, China. Methods: 100 cases of patients with AF of Han and 100 cases of patients with AF of Uyghur were selected as the experimental group, and 100 cases of patients with non-AF of Uyghur and non-AF of Han were selected as the control group. We amplified the AGT M235T site and AGT T174M site by PCR in 4 groups of patients, verified the polymorphism of the sites by gene sequencing, and compared their differences in each group. Results: The high risk factors for AF such as sex, left atrial diameter (LAD), right atrial diameter (RAD), and coronary heart disease were significantly different between the Han case group and the control group ($P < 0.05$). There were significant differences in age, LAD, RAD, coronary heart disease and smoking as contributors to AF between Uyghur case group and control group ($P < 0.05$). The genotype frequency distribution of AGT M235T and AGT T174M loci in the AF group and control group of Han and Uyghur was in accordance with Hardy-Weinberg equilibrium law test. There was a significant difference in genotype frequency and allele frequency of AGT M235T locus between Han group, Uyghur AF group and control group ($P < 0.05$). Conclusion: The AGT M235T and AGT T174M loci were associated with the occurrence of atrial fibrillation in the Han and Uyghur ethnic groups in Xinjiang.

Keywords: AGT M235T, AGT T174M, atrial fibrillation, Uyghur, Han

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. It is characterized by rapid atrial rate and uncoordinated atrial mechanical activity [1, 2]. AF often causes severe hemodynamic changes and cerebral embolism, and has a high incidence rate [3]. The prevalence rate of AF is 1% in the general population, but the prevalence of people aged > 65 years old is increased to 6% [4]. The mechanism of AF mainly includes the mechanisms of mechanics, electrophysiology, and molecular biology. Despite more research, the specific pathogenesis of AF is still unclear.

Most AF occurs in patients with organic heart disease, such as coronary heart disease, hypertension, or valvular heart disease, which is called acquired AF [5]. Generally, a certain degree of cardiac pathologic changes will accompany the occurrence of most acquired AF [6, 7]. However, there are many individuals with the same diseases who do not have AF, which indicates that there is a certain genetic susceptibility to AF. Therefore, in recent years, scholars have speculated that the occurrence of AF is closely related to genes. They have carried out a lot of research on the relationship between gene polymorphism and AF, and predicted and screened patients susceptible to AF according to gene polymorphisms, which provides new ideas and directions for the study of this disease [8, 9].

The incidence of AF increases with age. Epidemiologic studies show that the prevalence of AF in the United States is about 0.9% in adults, while the prevalence of AF in China is 0.77% in adults. However, the incidence rate of AF in

Uyghur people in Xinjiang, China is only 0.25%, the prevalence of AF in Uighur is significantly lower than that of other ethnic groups, and their clinical characteristics are different from those of Han people. This may not only be related to factors such as living environment and eating habits, but also to a large extent may be related to the genetic component of AF. With the development of the research on atrial fibrillation, it is believed that the occurrence of AF is closely related to a polymorphism of the angiotensin gene (AGT) [10].

Related studies have shown that renin-angiotensin-aldosterone system (RAAS) activity is associated with AF. AGT is an important gene in the RAAS. Angiotensin converting enzyme (ACE) can hydrolyze the peptide chain of the AGT terminal and make it into active ang II [11]. It is an effective vasopressin and aldosterone stimulating peptide. Many studies have proven that AGT may be one of the susceptibility genes for AF. Multiple reports have proved that the two sites of AGT M235T and AGT T174M are significantly correlated with AF [12, 13]. Previous studies have found that polymorphism of the AGT gene locus may cause certain differences in its distribution frequency due to different populations, regions, and races, and such differences may lead to differences in AF incidence and clinical heterogeneity among different regions and races [13].

Until now, there is no report about an association between AGT M235T and AGT T174M gene polymorphisms and AF in Chinese Uyghur and Han nationality. Therefore, in this study, Uighur and Han non-valvular AF patients in the Xinjiang region of China were selected as research objects to explore the relationship between the polymorphism of AGT M235T and AGT T174M gene locus and the occurrence and development of atrial fibrillation. Whether there are national differences between the two different nationalities is discussed and analyzed.

Materials and methods

Study subjects

A case-control study was used, and the data of all subjects were unknown before analysis. All blood samples of Uyghur and Han patients with AF and a healthy control group meeting the inclusion criteria were collected. All blood samples were obtained with the consent of the patients themselves or their authorized clients, and signed informed consent for sample collection in the Xinjiang major disease resource database of the First Affiliated Hospital of Xinjiang Medical University. This study was approved by the ethics committee of the First Affiliated Hospital of Xinjiang Medical University. During the whole study, all data of all patients were analyzed anonymously.

From January 2017 to December 2018, we selected 100 Han and Uighur patients who were hospitalized in the heart center of the First Affiliated Hospital of Xinjiang Medical University, and were definitely diagnosed with nonvalvular AF. There were 200 patients in the AF group. At the same time, 100 healthy Han and 100 Uyghur patients were selected from the heart center of the First Affiliated Hospital of Xinjiang Medical University in the same period. A total of 200 patients were selected as the control group.

Inclusion and exclusion criteria

Patients were included in the AF-group if they had a clear diagnosis of AF history in the hospital, and the surface ECG or dynamic ECG showed the rhythm of AF, and other arrhythmias were excluded; and the patients were all Han and Uygur patients. Patients with valvular heart disease, congenital heart disease, family history of intermarriage, hepatorenal disease, trauma within two weeks, inflammatory response, rheumatism and malignant tumor were excluded.

The control group comprised the Han and Uyghur patients who were hospitalized in the heart center of our hospital at the same time. The patients had no previous history of AF and ECG manifestations of AF; they had no blood relationship with the patients with AF; and the excluded patients had valvular heart disease, congenital heart disease, family history of intermarriage, hepatorenal disease, trauma within two weeks, inflammatory response, rheumatism or malignant tumor.

Experimental methods

Genomic DNA isolation

After fasting for one night, 5 ml of peripheral venous blood was taken from all subjects in an empty stomach and stored in anticoagulant

Table 1. Primers used in AGT M235T and AGT T174M polymerase chain reactions (PCRs)

Polymorphism	Primer sequences
AGT M235T (rs699)	P1: 5'-TTA GAA GGA AAC AGA CCA CA-3'
	P2: 3'-AAG GAT ACC CCT CAC ACT-5'
AGT T174M (rs4762)	P1: 5'-GTG ACC CAT TTT GCT TGT-3'
	P2: 3'-GGG CTA AGG GGA CTA ATA TC-5'

tubes containing 0.4% ethylenediaminetetraacetic acid (EDTA). Genomic DNA was isolated and purified from these samples using a genomic DNA extraction kit (TIANGEN Biotech Corporation, Beijing, China). Extracted DNA was stored at -20°C until use.

SNP genotyping

Each 20-μL polymerase chain reaction (PCR) included the following reagents: 10 μL 2X Es Taq master mix, 0.5 μL forward primer (10 pg/μL), 0.5 μL reverse primer (10 pg/μL), 2 μL template DNA (50 ng/μL), and RNase-free water up to 20 μL. Reactions were thoroughly mixed by slight agitation and amplification was carried out on an Applied Biosystems (Foster City, CA, USA) 2720 thermal cycler.

PCR amplification procedures: initial denaturation at 95°C for 3 min, 34 cycles of denaturation at 95°C for 3 min, annealing at 56.8°C for 3 min, extension at 72°C for 1 min. The final elongation is 72°C for 5 min. PCR products were stored at 4°C for 1 min. After the PCR reaction was finished, the amplified products of 10 μL were electrophoretic on 2% agarose gel, and the specificity and fragment size of PCR amplification products were observed. The primers used are shown in **Table 1**.

Statistical analysis

SPSS19.0 software was used for statistical analysis. The mean ± standard deviation was used for measurement data. Differences between AF patients and control subjects were analyzed by the Student t-test, and the χ^2 test was employed for count data. Hardy-Weinberg equilibrium (HWE) was used to test genetic balance. Unconditional logistic regression was used to correct the effect of high-risk factors of AF on the results of the study, and the association between the polymorphism of two gene loci and AF in Han and Uyghur was analyzed. *P* values < 0.05 were considered significant.

Results

Characteristics of the study participants

Differences of basic clinical characteristics between Uygur and Han nationality are shown in **Table 2**. Among Han subjects, the high risk factors for AF such as age, left atrial diameter (LAD), right atrial diameter (RAD), and coronary heart disease were significantly different between the case and control group ($P < 0.05$). There was no significant difference in other factors such as gender, body mass index (BMI), ejection fraction (EF), hypertension, diabetes, smoking, drinking, left ventricular end systolic diameter (LVESD), and left ventricular end diastolic diameter (LVEDD) between the case and control group ($P > 0.05$). In Uighur subjects, age, LAD, RAD, coronary heart disease, smoking, and other high-risk factors of AF were significantly different in the case and control group ($P < 0.05$), while other factors were not significantly different ($P > 0.05$).

PCR amplification

The gel image of the PCR products obtained is shown in **Figure 1**. The length of AGT M235T site is 156 bp (**Figure 1A**), and the length of AGT T174M site is 300 bp (**Figure 1B**). The DNA bands were clear and no non-specific bands were found, indicating that the amplification conditions were optimal and met the experimental requirements.

HWE test

HWE test was to verify whether the subjects participating in the experiment have a good population representation. The verification method was to calculate the genotype frequency of the AF and control group of the Han and Uygur nationalities in this study, and then calculate the *P* value by using the H-W balance formula. When $P > 0.05$, a genetic balance of the sample population was indicated, and the samples were from the same Mendelian population. In this study, both the genotype frequency distribution of AGT M235T and AGT-T174M loci were in line with the H-W balance. This indicates that the samples in this study conform to the genetic balance of the population and are well representative of the population (**Tables 3** and **4**).

Table 2. Comparison of the basic clinical features of Uyghur and Han individuals

	Han			Uyghur		
	AF (n = 100)	Control (n = 100)	*P* value	AF (n = 100)	Control (n = 100)	*P* value
Male/female	67/33	53/47	0.056	64/36	63/37	0.883
Age (years)	62.08±12.64	59.14±12.35	0.098	60.68±1.183	54.48±10.36	< 0.001*
BMI	25.04±3.44	25.10±3.34	0.901	27.85±4.58	27.38±3.55	0.419
LAD	38.14±6.911	32.80±3.55	< 0.001*	38.96±8.07	34.12±4.66	< 0.001*
RAD	33.16±3.26	35.79±5.51	< 0.001*	35.6±6.07	33.14±3.15	< 0.001*
EF	61.32±7.4	62.97±6.25	0.311	59.39±9.95	61.95±7.88	0.45
LVESD	31.89±4.03	33.11±6.57	0.068	34.75±8.45	33.36±6.49	0.194
LVEDD	49.50±6.37	48.72±4.13	0.053	50.7±8.06	50.14±5.78	0.573
Hypertension	54/100 (54%)	61/100 (61%)	0.317	54/100 (54%)	51/100 (51%)	0.671
Coronary heart disease	18/100 (18%)	55/100 (55%)	< 0.001*	40/100 (40%)	63/100 (63%)	0.001*
Diabetes	16/100 (16%)	25/100 (25%)	0.115	23/100 (23%)	19/100 (19%)	0.487
Smokers	14/100 (14%)	24/100 (24%)	0.071	9/100 (9%)	23/100 (23%)	0.007*
Drinkers	7/100 (7%)	13/100 (13%)	0.157	3/100 (3%)	6/100 (6%)	0.306

BMI = body mass index; LAD = left atrial dimension; RAD = right atrium dimension; EF = ejection fraction; LVESD = left ventricular end systolic diameter; LVEDD = left ventricular end diastolic diameter. *Significantly different compared to the control group.

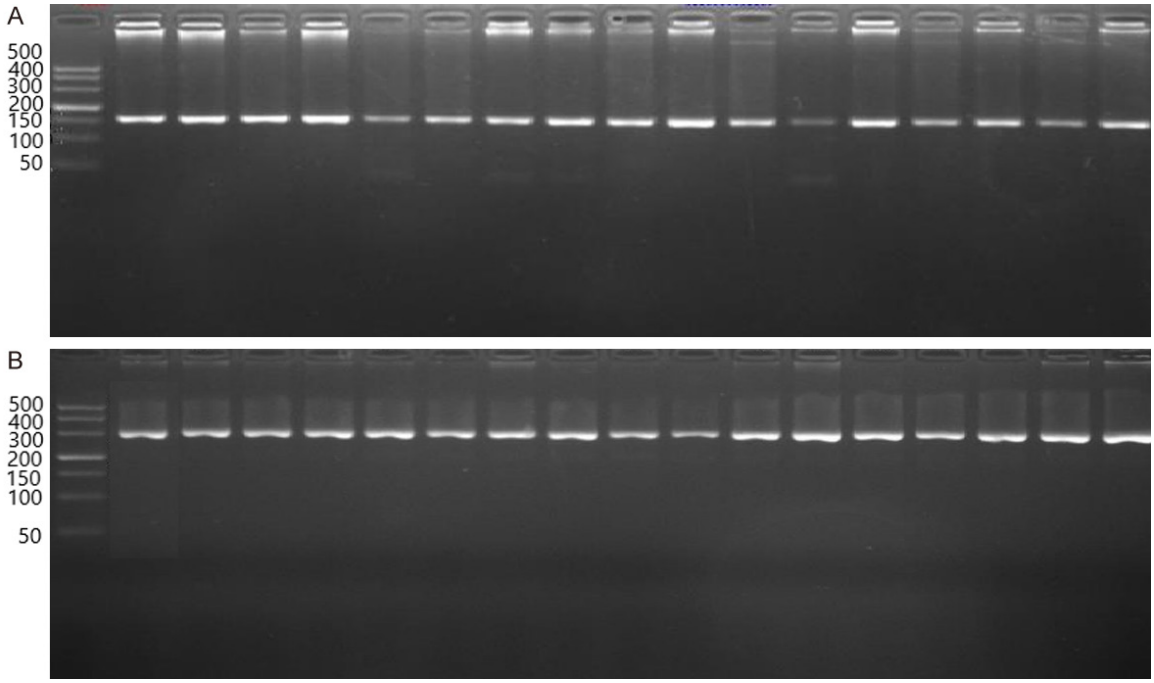

Figure 1. Electrophoresis of AGT M235T and AGT T174M polymerase chain reaction products.

AGT M235T and AGT T174M genotype and allele frequencies

Using Chromas software and Dnaman software to open the sequencing results, we found that there were three genotypes of AGT M235T: MM wild type, MT heterozygous type, and TT mutant (**Figure 2**). There are three genotypes of AGT T174M: TT wild type, TM heterozygote, and TT mutant (**Figure 3**). The mutation site of AGT M235T is that cytosine (C) replaces thymine base (T) at 704 of exon 2 of AGT gene, which makes methionine (M) at 235 of AGT gene mutate to threonine (T). The mutation site of

Table 3. Hardy-Weinberg equilibrium test of AGT M235T genotype frequencies in control and AF groups

Genotype	Controls				AF patients			
	Observed number	Expected number	χ^2 value	*P* value	Observed number	Expected number	χ^2 value	*P* value
Han								
MM	2	5	3.45	0.06	3	2	0.52	0.46
MT	42	36			23	25		
TT	56	59			74	73		
Uyghur								
MM	17	20	0.91	0.33	11	7	3.54	0.06
MT	54	49			32	39		
TT	29	31			57	53		

Table 4. Hardy-Weinberg equilibrium test of AGT T174M genotype frequencies in control and AF groups

Genotype	Controls				AF patients			
	Observed number	Expected number	χ^2 value	*P* value	Observed number	Expected number	χ^2 value	*P* value
Han								
MM	2	5	2.73	0.09	2	5	2.41	0.12
MT	40	34			39	34		
TT	58	61			59	61		
Uyghur								
MM	16	14	0.43	0.5	18	14	2.82	0.09
MT	44	48			39	47		
TT	40	38			43	39		

AGT T174M is that T replaces the C at the 521 position of the second exon of AGT gene, which makes T 174 of AGT gene mutate to M.

Genotype and allele frequency distribution of AGT M235T and AGT T174M

There was a significant difference in genotype frequency and allele frequency of the AGT M235T locus between the Han, and Uighur AF groups and control group ($P < 0.05$). Among them, the genotype frequency of AGT M235T in the AF group and control group was $\chi^2 = 8.246$, $P = 0.016$. The allele frequency was $\chi^2 = 4.743$, $P = 0.020$. The results of genotype frequency comparison of AGT M235T locus in Uighur AF group and control group were $\chi^2 = 16.030$, $P < 0.001$. Allele frequency comparison was $\chi^2 = 12.621$, $P < 0.001$ (**Table 5**). There was no significant difference in genotype frequency and allele frequency of AGT T174M between Han and Uighur AF group and control group ($P < 0.05$) (**Table 6**).

Correlation of AF with AGT M235T site and AGT T174M site

After adjusting for the high risk factors of AF (sex, age, hypertension, coronary heart disease, diabetes, smoking, drinking, LAD, RAD, BMI), the non-conditional logistic regression analysis found that the MT genotype of AGT M235T increased the relative risk of AF in Uighurs (genotype MT/MM: OR = 3.038, 95% CI = 1.259-7.326). However, the polymorphism of the AGT M235T locus did not increase the relative risk of the Han AF group compared with the Han control group. Polymorphism at AGT 174M did not increase the relative risk of AF in the Han and Uighur populations (**Table 7**). By comparing the results of unconditional logistic regression analysis between the AF group and case group of Hans, we found that AGT M235T and AGT T174M increased the relative risk of AF in Hans (OR = 1.515, 95% CI = 0.248-9.270; OR = 1.042, 95% CI = 0.594-1.829, respectively). This indicates that the AGT M235T and AGT

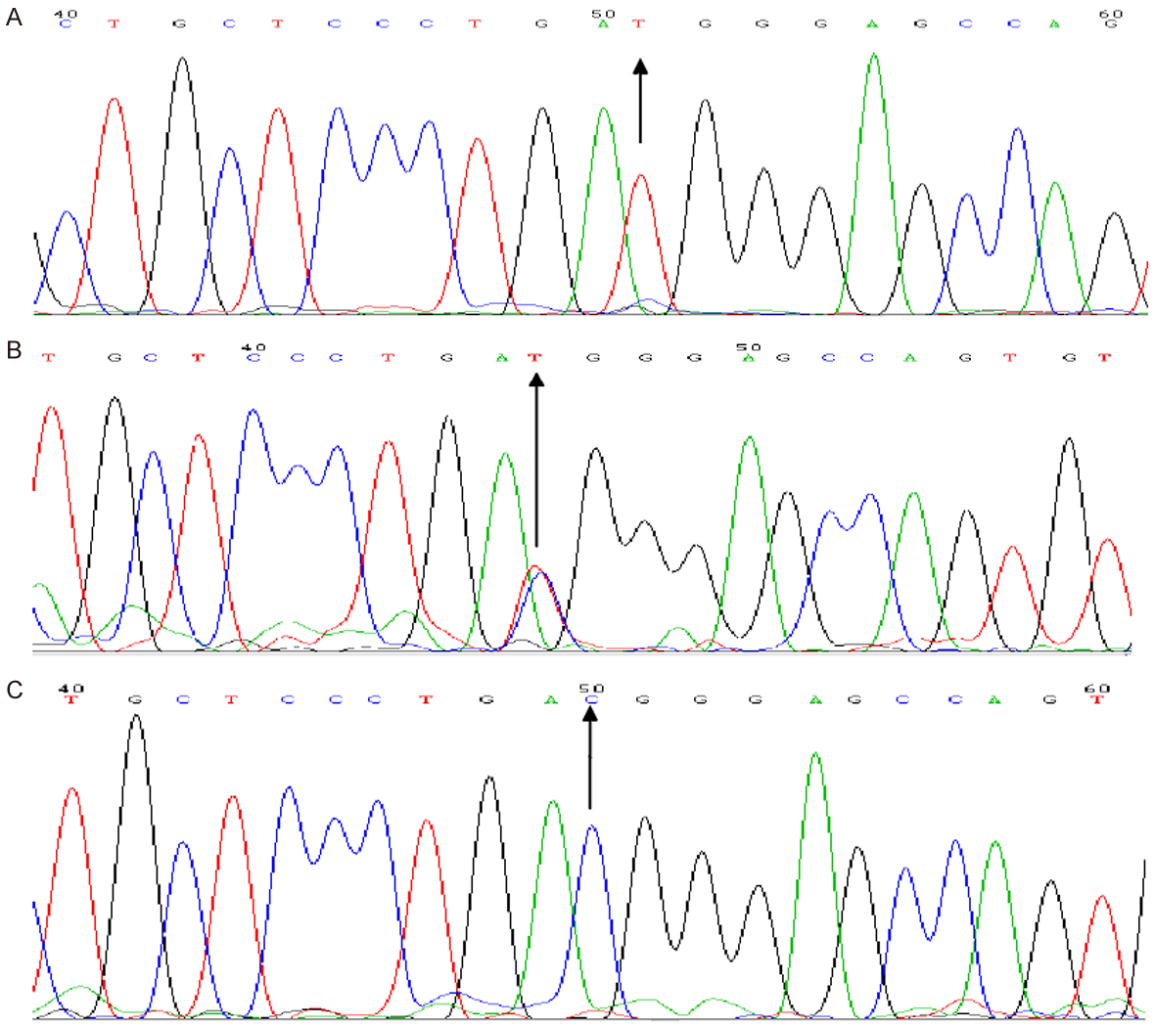

Figure 2. AGT M235T polymorphism sequencing results. A. Wild-type MM genotype; B. Heterozygous MT genotype; C. Mutant TT genotype. The arrow indicates the affected residue.

T174M loci both increase the risk of AF in Hans in the dominant mode, while neither the recessive mode nor the co-additive mode increases the risk of AF in Hans. The results of unconditional logistic regression analysis showed that AGT T174M increased the relative risk of AF in Uighurs under a dominant mode (OR = 1.132, 95% CI = 0.645-1.987) and co-additive mode (OR = 1.135, 95% CI = 0.642-2.007) (**Table 8**). This shows that AGT T174M can increase the risk of AF in Uighurs in both dominant and co-additive modes, but did not increase the risk of AF in recessive mode. However, AGT M235T did not increase the risk of AF in the dominant, recessive and co-additive modes.

Discussion

AF is not only a cardiovascular disease that can lead to many serious complications, but also an independent lethal factor, which can directly lead to the death of patients [14, 15]. The clinical symptoms and complications caused by AF seriously affect the quality of life of patients. Therefore, further study on the pathogenesis of AF is of great significance for the prevention and treatment of cardiovascular disease.

Dai et al. suggested that the activation of RAS system and the increase of ACE expression in atrial tissue play an important role in the pathogenesis of AF [16, 17]. Tsai first reported an association between RAS gene polymorphism and AF. It was found that AGT G-6A, M235T, T174M, and G-217A of AGT gene were significantly correlated with AF in a single locus analysis. Among them, the M235T allele in the second exon of AGT gene and the OR value of MM genotype/MT genotype in the AF group were

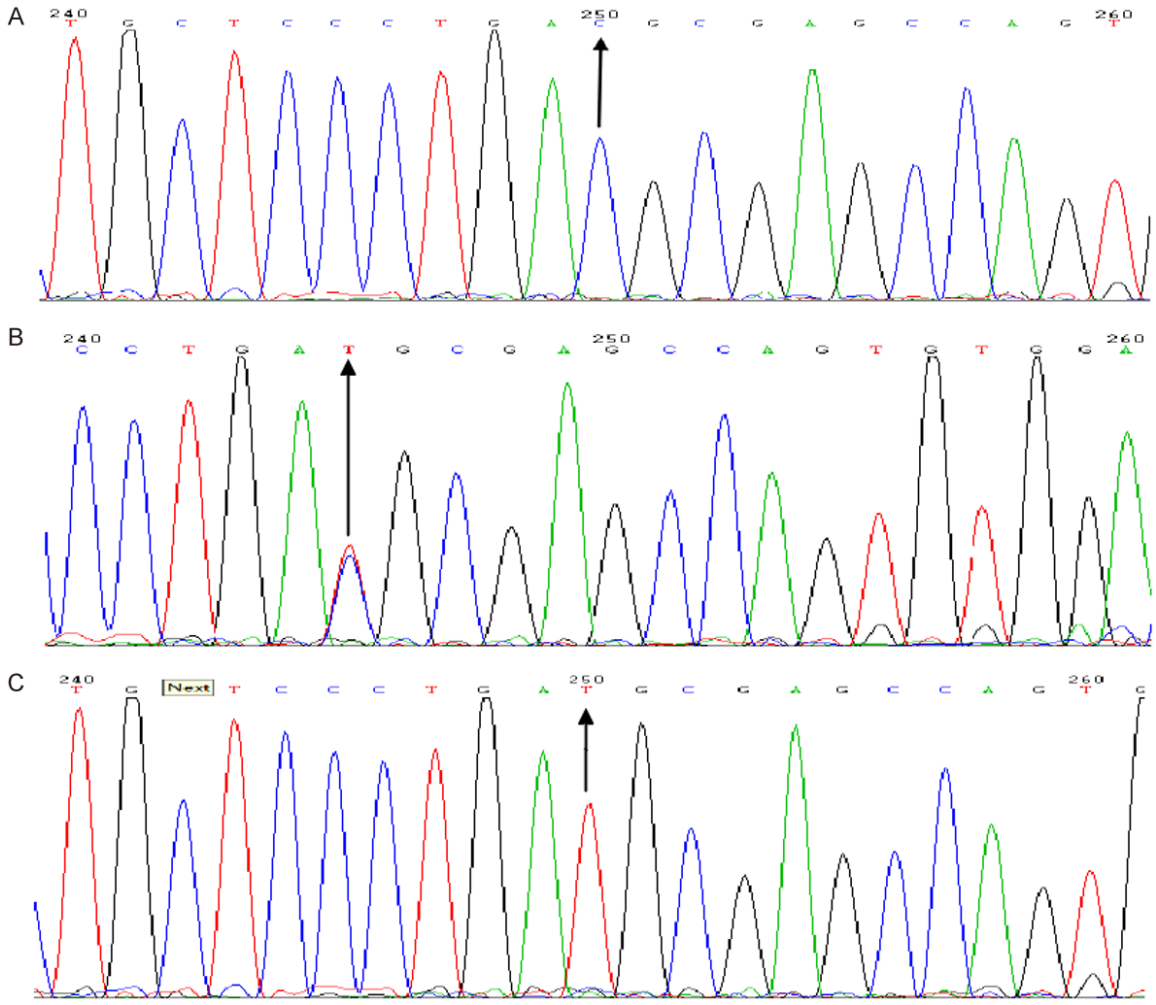

Figure 3. AGT T174M polymorphism sequencing results. A. Wild-type TT genotype; B. Heterozygous TM genotype; C. Mutant MM genotype. The arrow indicates the affected residue.

Table 5. Distribution of genotypes and alleles of AGT M235T loci

Genotype	AF (n%)	Control (n%)	χ^2 value	*P* value	Alleles	AF (n%)	Control (n%)	χ^2 value	*P* value
Han									
MM	3 (0.03)	2 (0.02)	8.246	0.016	M	29 (0.145)	46 (0.23)	4.743	0.020
MT	23 (0.023)	42 (0.42)							
TT	74 (0.74)	56 (0.56)			T	171 (0.855)	154 (0.77)		
Uyghur									
MM	11 (0.11)	17 (0.17)	16.030	< 0.001	M	54 (0.27)	88 (0.44)	12.621	< 0.001
MT	32 (0.32)	54 (0.54)							
TT	57 (0.57)	29 (0.29)			T	146 (0.73)	112 (0.56)		

significantly higher than those in the control group. Nudan et al. first explored and proved an association between AF and AGT gene polymorphisms in a Turkish population. The results showed that the proportion of T and TT alleles of M235T in the AF group was significantly higher than that in the control group [18]. The aim of this study was to investigate the relationship between AGT M235T, AGT T174M, and AF in patients with AF in Xinjiang, China. The results showed that the OR value of M235T genotype MT/MM was 3.038, which indicated that MT

Table 6. Distribution of genotypes and alleles of AGT T174M loci

Genotype	AF (n%)	Control (n%)	χ^2 value	*P* value	Alleles	AF (n%)	Control (n%)	χ^2 value	*P* value
Han									
TT	59 (0.59)	58 (0.58)	0.021	0.989	T	157 (0.785)	156 (0.78)	0.015	0.500
TM	39 (0.39)	40 (0.40)							
MM	2 (0.02)	2 (0.02)			M	171 (0.855)	44 (0.22)		
Uyghur									
TT	43 (0.43)	40 (0.40)	0.527	0.768	T	125 (0.625)	124 (0.62)	0.011	0.500
TM	39 (0.39)	44 (0.44)							
MM	18 (0.18)	16 (0.16)			M	75 (0.375)	76 (0.38)		

Table 7. Logistic analysis of AGT M235T and AGT T174M genotype

Loci	Genotype	AF (n%)	Control (n%)	OR (95% CI)
Han				
AGT M235T	MM	3 (0.03)	2 (0.02)	
	MT	23 (0.23)	42 (0.42)	0.881 (0.142-5.451)
	TT	74 (0.74)	56 (0.56)	0.365 (0.057-2.345)
AGT T174M	TT	59 (0.59)	58 (0.58)	
	TM	39 (0.39)	40 (0.40)	0.983 (0.134-7.215)
	MM	2 (0.02)	2 (0.02)	0.958 (0.542-1.696)
Uyghur				
AGT M235T	MM	11 (0.11)	17 (0.17)	
	MT	32 (0.32)	54 (0.54)	3.038 (1.259-7.326)
	TT	57 (0.57)	29 (0.29)	0.916 (0.382-2.198)
AGT T174sM	TT	43 (0.43)	40 (0.40)	
	TM	39 (0.39)	44 (0.44)	0.983 (0.134-7.215)
	MM	18 (0.18)	16 (0.16)	0.958 (0.542-1.696)

genotype of AGT M235T was related to AF. This is contrary to the research results of Tsai et al. In the population of AF of Hans, the dominant mode of AGT M235T and AGT T174M both increased the relative risk of AF of Hans, while the recessive mode and the co-additive mode of these two loci did not increase the probability of developing AF of Hans. In the Uighur AF population, both the dominant and co-additive mode of AGT T174M increased the relative risk of Uighur AF, while none of the three modes of AGT M235T in this study increased the probability of Uygur AF. Studies of the same gene locus in different ethnic groups have shown different results, possibly due to genetic differences in the subjects studied.

Zhao et al. found that patients in the AF group had larger LAD, LVESD, and smaller EF than those in the control group, suggesting that atrial enlargement plays an important role in the development of atrial fibrillation [19]. The famous Framingham study revealed that the enlargement of left atrium and the reduction of left ventricular systolic force increased the risk of AF [20]. In this study, when comparing the clinical data of Han and Uighur populations, we found that the high risk factors of AF, such as gender, LAD, RAD, and coronary heart disease, were significantly different between the Han AF group and the control group. The age, LAD, RAD, coronary heart disease, smoking, and other high-risk factors of AF were significantly different between the Uighur case group and control group. This indicates that the LAD in the AF group is significantly larger than that of the control group in both Han and Uighur groups, which is the same as the study results of Zhao and Framingham study. However, the results of this study did not show significant differences in LVESD and EF between the AF group and the control group, which may be related to the different distribution regions of the study population. Zhao et al. studied the Han population in Shanghai, China, while the subjects of the current study were the Han and Uighur populations in Xinjiang, China.

Conclusion

In summary, the AGT M235T locus had statistically significant differences in genotype frequency and allele frequency between the Han and Uighur AF groups and the control groups. There was no statistical difference in genotype frequency and allele frequency between the Han and Uighur AF groups and the control group. MT genotype at AGT M235T increased the relative risk of AF in Uygurs. Both the AGT

Table 8. Association analysis of AGT M235T site and AGT T174M site under genetic model

Loci	Genetic model	AF	Control	OR (95% CI)
Han				
AGT M235T	Dominant model (MT+TT/MM)	97/3	98/2	1.515 (0.248-9.270)
	Recessive model (TT/MT+MM)	74/26	56/44	0.447 (0.246-0.812)
	Co-additive model (MM+TT/MT)	77/23	58/42	0.412 (0.224-0.761)
AGT T174M	Dominant model (TM+MM/TT)	41/59	42/58	1.042 (0.594-1.829)
	Recessive model (MM/TM+TT)	2/98	2/98	1.000 (0.138-7.242)
	Co-additive model (TT+MM/TM)	61/39	59/41	0.920 (0.522-1.620)
Uyghur				
AGT M235T	Dominant model (MT+TT/MM)	89/11	83/17	0.603 (0.267-1.364)
	Recessive model (TT/MT+MM)	57/43	29/71	0.308 (0.172-0.554)
	Co-additive model (MM+TT/MT)	68/32	46/54	0.401 (0.225-0.713)
AGT T174M	Dominant model (TM+MM/TT)	57/43	60/40	1.132 (0.645-1.987)
	Recessive model (MM/TM+TT)	18/82	16/84	0.868 (0.414-1.817)
	Co-additive model (TT+MM/TM)	60/40	63/37	1.135 (0.642-2.007)

M235T and AGT T174M loci increased the relative risk of AF in the Hans in the dominant mode. The dominant and co-additive mode at AGT T174M increased the relative risk of AF in Uighurs. However, there are still many limitations to this study. First, the sample size of this study is insufficient, and the results of this study cannot represent people from other regions or other races, so it is necessary to include more and better quality people. Secondly, the results of this study only elucidated the association between AGT gene polymorphism and AF at the gene level, but did not explore the direct pathogenesis of the AGT gene to affect AF. Finally, the results of this study do not explore gene-gene interactions. Therefore, further studies are needed to explore the correlation between the AGT M235T and AGT T174M sites and AF.

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Disclosure of conflict of interest

None.

Address correspondence to: Muhuyati Wulasihan, Department of Cardiology, The First Affiliated Hospital of Xinjiang Medical University, Urumqi 830053, Xinjiang Uygur Autonomous Region, China. E-mail: Muhuyatiwulasihan@126.com

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