

Correlation between P-selectin rs1800807 and rs1800808 Gene polymorphisms and plasma soluble P-selectin concentrations in patients with atrial fibrillation complicated with thromboembolism in Xinjiang, China

Xiaoyun Ma, MM, Hailati Juledezi, MM, Zhiqiang Liu, MD*, Wulasihan Muhuyati, PhD*, Bakeyi Maerjiaen, MM, Pengyi He, MD

Abstract

This study is to investigate the relationship of P-selectin (Ps) gene rs1800807 and rs1800808 polymorphisms with plasma soluble P-selectin (sPs) in Han, Uygur, and Kazakh people with atrial fibrillation (AF) and thromboembolism (TE) in Xinjiang, China.

A total of 778 Han patients (including 131 patients with AF and TE, 229 patients with AF and 418 healthy individuals), 660 Uygur patients (including 118 patients with AF and TE, 232 patients with AF and 310 healthy individuals), and 505 Kazakh patients (including 42 patients with AF and TE, 156 patients with AF and 307 healthy individuals) were enrolled in this study. Polymerase chain reaction-restriction fragment length polymorphism and direct DNA sequence analysis were used to analyze the polymorphisms of rs1800807 and rs1800808 of Ps gene. ELISA was used to determine the plasma sPs level. The association between plasma sPs levels and Ps gene polymorphisms was further analyzed.

The sPs concentrations of GG genotype at rs1800807 locus in the Han, Uygur and Kazakh ethnic groups in Xinjiang, China were significantly higher than those of the CC genotype and CG genotype ($P < .05$). In the rs1800808 locus, plasma sPs concentrations of the heterozygous mutant CT genotypes in Han and Uygur populations were significantly higher than those in the CC and TT genotypes, whereas the plasma sPs concentrations in Kazakh TT genotypes were significantly higher than those in the CC and CT genotypes ($P < .05$). Among different ethnic groups, there were significant differences in sPs levels of rs1800807 and rs1800808 genotypes ($P < .05$).

Plasma sPs concentrations are associated with Ps genotypes and sPs concentration of the same genotype shows racial differences.

Abbreviations: AF = atrial fibrillation, BMI = body mass index, CRP = C-reactive protein, Ps = P-selectin, sPs = soluble P-selectin, TE = thromboembolism.

Keywords: atrial fibrillation, gene polymorphism, P-selectin, thromboembolism

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Department of Cardiology, the First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, PR China.

* Correspondence: Wulasihan Muhuyati, Zhiqiang Liu, Department of Cardiology, the First Affiliated Hospital of Xinjiang Medical University, No. 137 Liyushan Road, Urumqi 830054, PR China (e-mail: muhuyati@163.com, 119316539@qq.com).

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1. Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia.^[1–4] The report of cardiovascular disease in China 2018 indicates that the prevalence of AF in Chinese residents aged 35 years or older is 0.71%.^[5] There are more than 10 million patients with AF in China, and it is estimated that there will be more than 12 million AF patients in the United States by 2030.^[6] In Europe, AF is estimated to increase from the current 8.8 million to approximately 18 million in 2060.^[7–9] The prevalence of AF in patients with acute ischemic stroke increased from 16% in 2003 to 20% in 2014.^[10] Currently, the pathogenic mechanism of thromboembolism (TE) in patients with AF,^[11] including the common atrial TE and cerebral TE, has not been completely clear.

Etiological studies show that many factors may lead to the formation of thrombus in patients with AF.^[12,13] Among them, P-selectin (Ps) plays an important role in atherosclerosis inflammation and thrombosis.^[14,15] Ps gene polymorphisms and plasma soluble Ps (sPs) concentration increase are closely related with the risk of thrombosis.^[16–18] Barbaux et al^[19] found that the genetic polymorphisms of Ps, rs1800807, rs1800805, and rs6136, were associated with the serum levels of sPs in patients with coronary heart disease, and that the GG type of rs1800807, the AA type of rs1800805 and the TT type of rs6136 of sPs showed high serum concentrations. Ay et al^[20] found that the level of sPs in

thrombosis patients was significantly higher, and the sPs serum levels of the TP + PP genotype patients were significantly lower than the TT genotype patients, suggesting that TT genotype is a new genetic risk factor for venous thrombosis in Austrian Caucasian. Martea et al^[21] reported that Leu599Val and rs6136 gene polymorphisms could explain the level of sPs up to about 25%, and the Ps gene polymorphism of healthy people may significantly affect the level of sPs. It is reported that the plasma sPs levels and rs1800807 polymorphism have a significant correlation in Kazakh, Han and Uighur populations in Xinjiang,^[22–24] with the sPs level of GG genotype significantly higher than that of the CG + CC genotype. However, rs6136 polymorphism is not detected, though the thromboembolic events are associated with Ps gene polymorphisms and plasma sPs levels. Zeng et al^[25,26] suggested that the serum levels of sPs are closely related to rs1800807 polymorphism in the population of South China. It is suggested that thrombosis in patients with AF is associated with plasma sPs levels and Ps gene polymorphism,^[27] which may promote thromboembolic events by regulating plasma sPs levels.^[28] However, further studies are needed to verify this.

Xinjiang, China is a multi-ethnic area and the main ethnic groups include Han, Uygur, and Kazakh, which account for nearly 90% of the total population in Xinjiang. At present, there are few researches on the relationship between Ps gene polymorphism and sPs concentrations in ethnic minorities in Xinjiang of China. Polymorphism of Ps gene in different regions, races and populations may have some differences, and sPs concentrations may be also different in the blood due to the different genotypes. This study is to investigate the association between Ps gene polymorphisms and plasma sPs levels in Han, Uygur and Kazakh populations with non-valvular AF combined with TE in Xinjiang, China. Our findings may provide evidence for further study of the etiology of AF combined with TE.

2. Materials and methods

2.1. Subjects

The study subjects were hospitalized patients at the First Affiliated Hospital of Xinjiang Medical University from August, 2011 to December, 2018, and they were enrolled strictly according to the inclusion and exclusion criteria. A total of 131 Han patients, 118 Uyghur patients, and 42 Kazakh patients with non-valvular AF and TE were included as AF+TE group. A total of 229 Han patients, 232 Uyghur patients, and 156 Kazakh patients with non-valvular AF but without TE were included as AF group. Another 418 Han healthy individuals, 310 Uyghur healthy individuals and 307 Kazakh healthy individuals without AF or TE were included as healthy control group. The inclusion criteria were as follows:

- 1) For patients in AF + TE group, they were included according to the *Guidelines for the Treatment of Atrial Fibrillation* by American College of Cardiology (ACC) and American Heart Association (AHA) in 2019.^[29] Patients were diagnosed as paroxysmal or persistent AF by electrocardiogram or Holter, and confirmed as non-valvular AF by transthoracic echocardiography. The patients should meet one of the following conditions: Inpatients at department of cardiology, and were confirmed to have left atrial thrombosis or silt-like changes of left atrial blood by transesophageal ultrasound, or diagnosed as AF+TE-caused cerebral embolism by a senior neurologist with at least 10-year experience.

- 2) Patients with non-valvular AF but without thromboembolic events were included in AF group.
- 3) The subjects in the healthy control group were completely healthy people who received physical examination at the health examination center of the First Affiliated Hospital of Xinjiang Medical University during the study period.

The exclusion criteria were as follows: patients with valvular heart disease (abnormal heart valve structure or function by echocardiography), autoimmune diseases, acute/chronic infections, rheumatic activity (rheumatic fever, reactive arthritis, etc.), chronic liver disease, hematological diseases (leukemia, myeloma, etc.), nephropathy, malignant tumors, acute coronary syndromes, or oral administration of drugs such as contraceptives and diuretic drugs. Blood samples were collected, as well as the general clinical data including age, gender, smoking history, drinking history, body mass index (BMI), hypertension (blood pressure $\geq 140/90$ mmHg), C-reactive protein (CRP), fibrin, platelet count, etc. For the exclusion of other influencing factors associated with thrombosis, all enrolled subjects were required not to take any anticoagulant and antiplatelet aggregation drugs within 2 weeks prior to enrollment in the study. Written informed consent was obtained from every patient and the study was approved by the ethics review board of Xinjiang Medical University.

2.2. Blood sample collection

The blood samples of all included patients were collected on the morning of the next day of their hospitalization. For subjects of the healthy control group, 5 mL of venous blood was collected on the morning of the physical examination.

2.3. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)

The DNA was extracted using Genomic DNA extraction kit (Tiangen Biotech Co., Ltd., Beijing, China). The primers for rs1800807 and rs1800808 were designed using Primer 5.0 software (Premier Biosoft International, Palo Alto, CA), and synthesized by Sangon Biotech Co. (Shanghai, China). The genotyping was performed using PCR-RFLP. Briefly, the amplification procedure was: pre-denaturation at 95°C for 30 minutes, followed by 34 cycles of denaturation at 95°C for 30 seconds, annealing at 54.7°C (for rs1800807) or 56.6°C (for rs1800808) for 30 seconds, and extension at 72°C for 60 seconds, and final extension at 72°C for 5 minutes. The primer sequence was listed in the supplementary Table S1, <http://links.lww.com/MD/D682>. The PCR products were then incubated with endonucleases for 16 hours at 37°C, and then subjected to 2% agarose gel electrophoresis. An exact homozygous genotype served as a control for the digestion reaction. According to the results of PCR amplification and enzymatic cleavage, 20 gene samples were randomly selected from each gene locus and sequenced by Sangon Biotech (Shanghai) Co., Ltd (Shanghai, China). The results of gene polymorphism DNA sequencing and restriction enzyme digestion were compared again to verify whether the results are consistent.

2.4. Determination of concentration

The plasma was isolated from the peripheral venous blood by centrifugation. The sPs concentration in the plasma was

determined by an ELISA kit (Invitrogen Co. Waltham, MT) according to the manufacturer’s instructions. Plasma sPs reference value is 0 to 97 pg/mL.

2.5. Statistical analysis

SPSS 25.0 (SPSS Inc., Chicago, IL) was used for data analysis. The measurement data were non-normally distributed and thus expressed as (median, quartile), that is, (M, Q), and analyzed by non-parametric test (Wilcoxon rank sum test for 2 group comparison and Kruskal-Wallis H test for multi group comparison). For the counting data, frequency (n, %) was used to describe the data, and Chi-square test was used for data analysis. The genotypes and allele frequencies were calculated and analyzed by Chi-square test. The Hardy-Weinberg equilibrium test was used to analyze the population representativeness of the samples. A P value of $P < .05$ was considered as statistically significant.

3. Results

3.1. General data

The general data of the Han, Uygur, and Kazakh populations were compared. There were significant differences in age, BMI, systolic blood pressure, diastolic blood pressure, CRP, platelet and fibrinogen among the three groups of Han population ($P < .05$). Compared with the control group, the age, BMI, systolic blood pressure, diastolic blood pressure, CRP, platelet, and fibrinogen of the AF+TE group were all statistically different ($P < .05$). Compared with the control group, the age, BMI, systolic blood pressure and platelet of the AF group were statistically different ($P < .05$). Compared with the AF group, the BMI, systolic blood pressure, CRP, and fibrinogen of the AF+TE group were all statistically different ($P < .05$, Table 1).

There were significant differences in age, BMI, systolic blood pressure, diastolic blood pressure, CRP, platelet and fibrinogen in the three groups of Uygur ($P < .05$). Compared with the control group, the age, systolic blood pressure, CRP, platelet and fibrinogen of the AF+TE group were all statistically different ($P < .05$). Compared with the control group, the age, systolic blood pressure, diastolic blood pressure, CRP, platelet and fibrinogen were statistically different ($P < .05$). Compared with the AF group, the diastolic blood pressure, platelet and CRP of the AF+TE group were statistically different ($P < .05$, Table 2).

There were significant differences in BMI, systolic blood pressure, diastolic blood pressure and fibrinogen in the 3 groups of Kazakh population ($P < .05$). Compared with the control group, the BMI and fibrinogen of the AF+TE group were statistically different ($P < .05$). Compared with the control group, the BMI, systolic blood pressure and diastolic blood pressure of the AF group were statistically different ($P < .05$). Compared with the AF group, the BMI and fibrinogen of the AF+TE group were statistically different ($P < .05$, Table 3).

In the Han and the Uygur populations, there were significant differences in smoking and drinking among the three groups of each population ($P < .05$), but no significant difference in gender ($P > .05$). For the 3 groups of patients in the Kazakh population, there was no significant difference in gender, smoking and drinking (Table 4).

3.2. Ps genotype polymorphism analysis and its distribution in Han, Uygur, and Kazakh populations

In the preliminary experiment, we found that the polymorphisms of the Ps gene promoters of rs1800807 in Han, Uygur and Kazakh populations in Xinjiang, China, were wild-type homozygous CC, heterozygous CG, and mutant homozygous GG

Table 1
The clinical and laboratory characteristics of Han Patients.

Characteristics	AF+TE group (n=131)	AF group (n=229)	Control group (n=418)	P	P (Pairwise)
Age (years)	(59.00, 22.00)	(63.00, 17.00)	(56.00, 18.00)	<.01	<.01* <.01† 1.00‡
Body mass index (kg/m ²)	(27.82, 5.02)	(26.56, 5.74)	(24.19, 5.11)	<.01	<.01* <.01† .05‡
Systolic blood pressure (mmHg)	(130.00, 16.00)	(120.00, 30.00)	(122.00, 18.00)	<.01	<.01* <.01† <.01‡
Diastolic blood pressure (mmHg)	(81.00, 13.00)	(80.00, 16.00)	(79.00, 18.00)	.05	.08* 1.00† .06‡
Platelet (*10 ⁹ /L)	(278.00, 35.00)	(278.00, 45.00)	(267.00, 44.00)	<.01	<.01* <.01† .39‡
C-reactive protein (mg/L)	(4.49, 2.35)	(3.33, 2.89)	(3.51, 2.46)	<.01	.01* .35† <.01‡
Fibrinogen (mg/dL)	(4.41, 1.07)	(3.57, 1.33)	(3.67, 1.78)	<.01	<.01* 1.00† <.01‡

The measurement data were non-normally distributed and thus expressed as (median, quartile), that is, (M, Q), and analyzed by non-parametric test (Wilcoxon rank sum test for 2 group comparison and Kruskal-Wallis H test for multi group comparison).

* represents comparison between AF+TE and control groups.

† represents comparison between AF and control groups.

‡ represents comparison between AF+TE and AF groups.

Table 2
The clinical and laboratory characteristics of Uyghur patients.

Characteristics	AF+TE group (n=118)	AF group (n=232)	Control group (n=310)	P	P (Pairwise)
Age (years)	(65.50, 16.00)	(64.00, 18.00)	(52.00, 20.30)	<.01	<.01* <.01† .19‡
Body mass index (kg/m ²)	(29.43, 2.22)	(29.01, 5.58)	(28.03, 7.86)	.04	.07* 1.00† .06‡
Systolic blood pressure (mmHg)	(132.50, 22.30)	(135.00, 30.00)	(130.00, 20.00)	<.01	.01* <.01† 1.00‡
Diastolic blood pressure (mmHg)	(80.00, 16.30)	(80.00, 18.00)	(80.00, 10.00)	.04	1.00* <.01† .02‡
Platelet (*10 ⁹ /L)	(288.00, 75.50)	(230.00, 68.00)	(256.00, 55.00)	<.01	<.01* <.01† <.01‡
C-reactive protein (mg/L)	(3.32, 1.37)	(2.50, 1.25)	(2.34, 1.42)	<.01	<.01* .02† <.01‡
Fibrinogen (mg/dL)	(4.01, 1.36)	(3.98, 1.76)	(3.24, 1.91)	<.01	<.01* <.01† .23‡

The measurement data were non-normally distributed and thus expressed as (median, quartile), that is, (M, Q), and analyzed by non-parametric test (Wilcoxon rank sum test for 2 group comparison and Kruskal-Wallis H test for multi group comparison).

* represents comparison between AF+TE and control groups.

† represents comparison between AF and control groups.

‡ represents comparison between AF+TE and AF groups.

types. The polymorphism of the Ps gene promoters of rs1800808 were wild-type homozygous CC, heterozygous CT and mutant homozygous TT types. In the rs1800807 group, there were significant differences in gene types between different groups of the same ethnic population (Han, Uyghur, and Kazakh) ($P < .05$). In the rs1800808 group, the genetic types between different

groups of the Han and Kazakh populations were significantly different ($P < .05$). There were no significant differences in gene types between different groups of Uyghur (Table 5). The genotype distributions of rs1800807 (Table 6) and rs1800808 (Table 7) were consistent with the Hardy-Weinberg equilibrium, suggesting that the samples have good population representativeness.

Table 3
The clinical and laboratory characteristics of Kazakh patients.

Characteristics	AF+TE group (n=42)	AF group (n=156)	Control group (n=307)	P	P (Pairwise)
Age (years)	(54.00, 26.00)	(51.00, 20.00)	(52.00, 21.00)	.16	
Body mass index (kg/m ²)	(31.17, 8.07)	(24.84, 6.80)	(28.03, 7.56)	.04	.02* <.01† <.01‡
Systolic blood pressure (mmHg)	(130.00, 22.00)	(135.00, 28.00)	(130.00, 20.00)	<.01	.41* <.01† .16‡
Diastolic blood pressure (mmHg)	(80.00, 10.00)	(88.00, 20.00)	(80.00, 10.00)	.04	.15* <.01† .21‡
Platelet (*10 ⁹ /L)	(289.00, 42.00)	(256.00, 55.00)	(256.00, 44.00)	<.01	<.01* 1.00† .01‡
C-reactive protein (mg/L)	(2.37, 1.23)	(2.37, 1.31)	(2.40, 1.31)	.97	
Fibrinogen (mg/dL)	(5.00, 1.17)	(3.62, 2.11)	(3.57, 2.22)	<0.01	<.01* 1.00† .01‡

The measurement data were non-normally distributed and thus expressed as (median, quartile), that is, (M, Q), and analyzed by non-parametric test (Wilcoxon rank sum test for 2 group comparison and Kruskal-Wallis H test for multi group comparison).

* represents comparison between AF+TE and control groups.

† represents comparison between AF and control groups.

‡ represents comparison between AF+TE and AF groups.

Table 4
Demographic and clinical characteristics of the participants.

Ethnic group	Characteristics	AF+TE group	AF group	Control group	P
Han	Smokers n (%)	59 (45.04)	106 (46.29)	126 (30.14)	<.01
	Gender (Male, n (%))	75 (57.25)	151 (65.94)	249 (59.57)	.17
	Drinkers n (%)	42 (32.06)	126 (55.02)	119 (28.47)	<.01
Uygur	Smokers n (%)	48 (40.67)	109 (46.98)	95 (30.65)	<.01
	Gender (Male, n (%))	70 (59.32)	133 (57.33)	205 (61.13)	.09
	Drinkers n (%)	47 (39.83)	104 (44.83)	82 (26.45)	<.01
Kazakh	Smokers n (%)	10 (23.81)	52 (33.33)	93 (30.29)	.48
	Gender (Male, n (%))	23 (54.76)	102 (65.38)	203 (66.12)	.34
	Drinkers n (%)	7 (16.67)	25 (16.03)	67 (21.82)	.29

Counting data was expressed as frequency (n, %) and analyzed with Chi-square test.

3.3. The relationship between Ps gene polymorphism and sPs concentration

As shown in Table 8, in Han population of Xinjiang, plasma sPs concentration ((43.00, 27.00) pg/mL) of rs1800807 GG homozygous mutant genotype was significantly higher than that of the wild-type CC ((30.00, 18.50) pg/mL) and heterozygous mutant CG ((36.00, 19.00) pg/mL) genotypes ($P < .001$). The plasma sPs concentration ((42.00, 19.0) pg/mL) of rs1800808 CT heterozygous mutant genotype was significantly higher than that

of the wild-type CC ((39.00, 15.00) pg/mL) and homozygous mutant TT ((40.00, 15.00) pg/mL) genotypes ($P < .001$).

In Uygur population of Xinjiang, plasma sPs concentration ((42.00, 16.50) pg/mL) of rs1800807 GG homozygous mutant genotype was significantly higher than that of the wild-type CC ((29.00, 18.00) pg/mL) and heterozygous mutant CG ((32.00, 19.00) pg/mL) genotypes ($P < .001$). The plasma sPs concentration ((38.00, 17.80) pg/mL) of rs1800808 CT heterozygous mutant genotype was significantly higher than that of the

Table 5
Comparison of genotyping frequencies among Han, Uygur, and Kazak populations.

SNPs	Ethnic group	Genotype	AF+TE group n (%)	AF group n (%)	Control group n (%)	P	
rs1800807	Han	CC	23 (17.56)	51 (22.27)	39 (9.33)	<.01	
		CG	59 (45.04)	109 (47.60)	199 (47.61)		
		GG	49 (37.40)	69 (30.13)	180 (43.06)		
	Uygur	CC	26 (22.03)	38 (16.38)	96 (30.97)		<.01
		CG	72 (61.02)	126 (54.31)	125 (40.32)		
		GG	20 (16.95)	68 (29.31)	89 (28.71)		
	Kazakh	CC	4 (9.52)	31 (19.87)	113 (36.80)		<.01
		CG	9 (21.43)	98 (62.82)	138 (44.96)		
		GG	29 (69.05)	27 (17.31)	56 (18.24)		
rs1800808	Han	CC	23 (17.56)	19 (8.30)	162 (38.76)	<.01	
		CT	61 (46.56)	99 (43.23)	122 (29.19)		
		TT	47 (35.88)	111 (48.47)	134 (32.05)		
	Uygur	CC	17 (14.41)	17 (7.33)	40 (12.90)		.22
		CT	52 (44.07)	112 (48.28)	140 (45.16)		
		TT	49 (41.5)	103 (44.39)	130 (41.94)		
	Kazakh	CC	8 (19.05)	11 (7.05)	21 (6.84)		.01
		CT	14 (33.33)	48 (30.77)	132 (43.00)		
		TT	20 (47.62)	97 (62.18)	154 (50.16)		

Counting data was expressed as frequency (n, %) and analyzed with Chi-square test.

Table 6
Hardy-Weinberg equilibrium Tests of the loci rs1800807 among subjects.

Ethnic group	Genotype	Number of observations	Expected value	χ^2	P
Han	GG	298	298	1.17	1.00
	GC	367	367		
	CC	113	113		
Uygur	GG	177	174	0.27	.60
	GC	323	330		
	CC	160	157		
Kazakh	GG	112	109	0.31	.58
	GC	245	251		
	CC	148	145		

Chi-square test was performed. $P > .05$ indicates that the sample has a representative population.

Table 7
Hardy-Weinberg equilibrium tests of the loci rs1800808 among subjects.

Ethnic group	Genotype	Number of observations	Expected value	χ^2	P
Han	TT	292	240	54.91	1.26
	TC	282	384		
	CC	204	152		
Uygur	TT	282	285	0.34	.36
	TC	304	297		
	CC	74	77		
Kazak	TT	271	268	0.41	.52
	TC	194	200		
	CC	40	37		

Chi-square test was performed. $P > .05$ indicates that the sample has a representative population.

wild-type CC ((30.00, 20.50) pg/mL) and homozygous mutant TT ((32.00, 20.00) pg/mL) genotypes ($P < .05$, Table 8).

Furthermore, Table 8 showed that plasma sPs concentration ((42.23, 10.00) pg/mL) of rs1800807 GG homozygous mutant genotype in Kazakh population of Xinjiang was significantly higher than that of the wild-type CC ((40.00, 16.25) pg/mL) and heterozygous mutant CG ((39.00, 15.30) pg/mL) genotypes ($P < .05$). The plasma sPs concentration ((40.00, 6.00) pg/mL) of rs1800808 TT homozygous mutant genotype was significantly higher than that of the wild-type CC (30.00, 17.54) pg/mL) and heterozygous mutant CT ((40.00, 16.50) pg/mL) genotypes ($P < .05$).

For the rs1800807 gene, there was a significant difference in the expression level of sPs between different ethnic populations with the same genotype ($P < .05$), among which the concentration of sPs in Kazakh was higher than those of Han and Uygur with the CC and CG genotypes, while for the GG genotype, the sPs level of Han population was the highest (Table 9).

For the rs1800808 gene, there was also a significant difference in the expression level of sPs between different ethnic populations with the same genotype ($P < .05$), among which the concentration of sPs in Han population was higher than those of Kazaka and Uygur (Table 9).

Taken together, plasma sPs levels of the rs1800807 mutant GG genotype and rs1800808 heterozygous CT and mutant TT genotypes were significantly higher, suggesting that plasma sPs concentrations in the Han, Uygur and Kazakh populations are related to the Ps genotype.

4. Discussion

AF is becoming a growing epidemic.^[1–4] AF not only leads to a decline in quality of life, but also increases the risk of stroke and death. It is reported that up to 125,000 strokes per year in the USA are attributed to AF, accounting for 40% of patients with stroke.^[30,31]

Table 8
Relationship between Ps gene polymorphism and sPs concentration among Han, Uygur, and Kazak populations.

SNPs	Ethnic group	Genotype	Plasma sPs (pg/mL) (M, Q)	P	P (Pairwise)
rs1800807	Han	CC	(30.00, 18.50)	<.01	<.01*
		CG	(36.00, 19.00)		<.01†
		GG	(43.00, 27.00)		.26‡
	Uygur	CC	(29.00, 18.00)		<.01*
		CG	(32.00, 19.00)		<.01†
		GG	(42.00, 16.50)		.89‡
	Kazakh	CC	(40.00, 16.25)		<.01*
		CG	(39.00, 15.30)		<.01†
		GG	(42.23, 10.00)		1.00‡
rs1800808	Han	CC	(39.00, 15.00)	<.01	1.00§
		CT	(42.00, 19.0)		<.01
		TT	(40.00, 15.00)		<.01¶
	Uygur	CC	(30.00, 20.50)		.01§
		CT	(38.00, 17.80)		.01
		TT	(32.00, 20.00)		.01¶
	Kazakh	CC	(30.00, 17.54)		<.01§
		CT	(40.00, 16.50)		.01
		TT	(40.00, 6.00)		.01¶

The measurement data were non-normally distributed and thus expressed as (median, quartile), that is, (M, Q), and analyzed by non-parametric test (Wilcoxon rank sum test for 2 group comparison and Kruskal-Wallis H test for multi group comparison).

* represents the comparison between CC and GG.

† represents the comparison between CG and GG.

‡ represents the comparison between CC and CG.

§ represents the comparison between CC and TT.

|| represents the comparison between CT and TT.

¶ represents the comparison between CC and CT.

Table 9
The plasma sPs levels in Han, Uyghur and Kazakh populations.

SNPs	Ethnic	Plasma sPs (pg/mL)	P	P (Pairwise)
rs1800807 CC	Han	(30.00, 19.00)	<.01	.01*
	Uyghur	(29.00, 18.00)		<.01†
	Kazakh	(40.00, 13.00)		.66‡
rs1800807 GG	Han	(43.00, 28.00)	<.01	<.01*
	Uyghur	(42.00, 17.00)		.71†
	Kazakh	(40.00, 17.00)		<.01‡
rs1800807 CG	Han	(38.00, 16.00)	<.01	.23*
	Uyghur	(32.00, 19.00)		<.01†
	Kazakh	(40.00, 6.00)		.01‡
rs1800808 CC	Han	(39.00, 15.00)	<.01	.03
	Uyghur	(30.00, 21.00)		1.00†
	Kazakh	(30.00, 18.00)		.01‡
rs1800808 TT	Han	(40.00, 15.00)	<.01	.01*
	Uyghur	(32.00, 20.00)		<.01†
	Kazakh	(40.00, 6.00)		<.01‡
rs1800808 CT	Han	(42.00, 19.00)	<.01	<.01*
	Uyghur	(38.00, 18.00)		1.00†
	Kazakh	(40.00, 17.00)		<.01‡

The measurement data were non-normally distributed and thus expressed as (median, quartile), that is, (M, Q), and analyzed by non-parametric test (Wilcoxon rank sum test for 2 group comparison and Kruskal-Wallis H test for multi group comparison).

* represents the comparison between Han and Kazakh.

† represents the comparison between Uyghur and Kazakh.

‡ represents the comparison the comparison between Han and Uyghur.

The main risk of AF is thrombosis. First, the loss of mechanical contraction function of atrium and the presence of blood stagnation makes AF patients prone to thrombosis. If the blood clot falls off, it will circulate with blood and may cause cerebral infarction or circulatory embolism, resulting in disability and death. The prevalence of AF among patients admitted with acute ischemic stroke has increased from 16% in 2003 to 20% in 2014.^[11] The incidence of thromboembolic events in patients with AF is 5 times higher than that in normal people, and the mortality, disability, and recurrence rates associated with AF are high.^[11,30-34] The incidence of stroke caused by AF rose sharply from 1.5% at 50-59 to 23.5% at 80-89.^[35] Second, the loss of effective atrial systolic function and long-term fast heart rate in patients with AF can lead to tachycardia cardiomyopathy, which eventually leads to decreased heart function and even heart failure. In addition, AF itself can also increase mortality. Patients with AF have thrombosis and are in prethrombotic states.^[11] One of the main causes of thrombosis is the increased expression of platelet Ps.^[30]

Ps is an inflammatory marker expressed in the particles of platelets and the Weibelpalade body of endothelial cells. It is also expressed in most tissues of human body, such as heart, liver, colon, kidney vascular endothelium and platelets, but the level is low. When stimulated by hypoxia, free radicals, thrombin, etc., Ps would be expressed on the cell membrane of platelets or endothelial cells during degranulation, and thus mediate the initial adhesion between leukocytes and endothelial cells, playing a central role in inflammatory response and thrombosis.^[36]

In China, the relationship between Ps gene polymorphism and AF is mainly focused on the Han population. However, China has a vast territory and a large population. The population of Xinjiang in western China is composed of different ethnic groups, mainly including Han, Uyghur and Kazakh. The living environment and dietary structure of different ethnic groups are different. Therefore, whether the correlation between Ps gene polymorphism and AF differs among different ethnic groups has attracted much attention. For example, Zhang et al found that increased Ps concentration was an independent risk factor for pre-thrombotic

non-valvular AF in Kazakh population of Xinjiang.^[37] Bai et al found that plasma sPs levels and Ps gene polymorphisms were associated with AF combined with TE in Uyghur population of Xinjiang.^[23] Based on these findings, this study analyzed the relationship between the Ps gene polymorphisms and the plasma sPs concentration in the Han, Uyghur and Kazakh ethnic groups in Xinjiang, China. The plasma sPs concentration of rs1800807 GG genotype in Han, Uyghur and Kazakh was significantly higher than that of the CC and CG genotypes. For the rs1800808 gene, the plasma sPs concentration of the heterozygous mutant CT genotype was significantly higher than that of the CC and TT genotypes in the Han and Uyghur populations. However, in the Kazakh population, the plasma sPs level of the TT genotype was significantly higher than those of the CC and CT genotypes. The plasma sPs concentration in the Han, Uyghur and Kazakh populations was associated with the Ps genotype. The sPs concentration of the same genotype showed racial differences. Compared with this study, some studies reported opposite results. Zeng et al^[25,26] found no correlation between serum sPs level and rs1800808 in the population of South China, which may be due to geographic and ethnic differences. Carter et al^[38] showed that serum sPs level was significantly associated with rs6136 gene polymorphism, but not with rs1800805, rs1800807, and rs1800808 gene polymorphisms. Despite the inconsistencies in the above experiments, it is suggested that the Ps gene polymorphism is associated with serum levels of sPs. The above studies show that not all populations have similar results, and poor reproducibility is a common problem in complex disease researches. The possible reasons are:

1. the effect of gene polymorphism alone is weak, and its effect is closely related to genetic background, environmental factors and regional areas;
2. there may be linkage disequilibrium between different genes, which may affect the consistency of the research results;
3. the difference in the statistical methods;
4. differences in experimental design, such as insufficient sample size, non-rigorous control design, sampling error and group

stratification, can lead to inconsistencies in the results of susceptibility genes.

This study has some limitations. First, the sample size was relatively small. Second, this study was conducted on local population and thus the findings were limited to local population. Further studies with larger sample size and on multiple areas and centers are needed.

In conclusion, plasma sPs concentrations are associated with Ps genotypes in Han, Uygur and Kazak populations of Xinjiang, China. The sPs concentration of the same genotype shows racial differences. Ps gene polymorphism may be a risk factor for thrombotic events independent of traditional susceptibility factors, or may be a genetic susceptibility marker for patients with AF, who are susceptible to TE. Our findings may provide evidence for further investigating whether there is genetic susceptibility to AF complicated with TE and may provide an experimental basis for the early prevention, diagnosis and treatment of AF combined with TE.

Author contributions

Conceptualization: Zhiqiang Liu, Wulasihan Muhuyati.

Methodology: Xiaoyun Ma, Hailati Juledezi.

Software: Xiaoyun Ma, Hailati Juledezi, Bakeyi Maerjiaen, Pengyi He.

Writing – original draft: Xiaoyun Ma, Hailati Juledezi, Bakeyi Maerjiaen, Pengyi He.

Writing – review & editing: Zhiqiang Liu, Wulasihan Muhuyati.

Correction

The grant number has been changed in the footnote on page 1.

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