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Original Article

Relationship between polymorphisms of C893T gene of platelet membrane receptor P2Y1 and cerebral infarction

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Abstract: Objective: This study aimed to determine the relationship between polymorphisms of C893T gene of platelet membrane receptor P2Y1 and cerebral infarction (CI) in Han population of North Shandong Province of China. Methods: A case-control study of 162 healthy people (the normal contrast group) and 185 CI patients confirmed by computed tomography or magnetic resonance imaging (CI group) was conducted. The polymorphisms were tested by polymerase chain reaction and restriction fragment length polymorphism analysis (PCR-RFLP). The distribution characteristics in normal people and CI patients, as well as the relationship between the polymorphisms of C893T gene and ischemic stroke, were analyzed. Results: No significant differences in gender composition and age were found between the contrast group and CI group ($P>0.05$). By contrast, significant differences were found in smoking, systolic pressure, diastolic blood pressure, and plasma fibrinogen level between contrast and CI groups ($P<0.05$ or $P<0.01$). Genotyping revealed 149 carriers of the wild-type CC genotype and 36 carriers of the mutational T allele of P2Y1 C893T in the CI group, and 148 carriers of the wild-type CC genotype and 14 carriers of the mutational T allele of P2Y1 C893T in contrast group. The TC/TT gene frequencies (19.46%) in the CI group was much higher ($X^2=8.195$, $P<0.01$) than that of contrast group (8.64%). The frequencies of T allele in the CI and contrast groups were 10.81% and 4.63%, respectively, showing significant difference ($X^2=9.045$, $P<0.01$). Multiple logistic regression analysis showed that factors associated with CI include systolic blood pressure, plasma fibrinogen level, and carrying -893T gene. After controlling for potential confounding factors, -893T allele carriers had a 2.065-fold increased risk for CI (OR=2.065, 95% confidence interval: 1.011-4.218, $P=0.046$) compared with non-carriers. Conclusion: Platelet membrane receptor P2Y1 C893T gene TC/TT is likely a risk factor of ischemic stroke.

Keywords: Platelet membrane receptors, P2Y1 gene polymorphism, cerebral infarction

Introduction

Adenosine diphosphate (ADP) is an important medium for platelet aggregation, and its receptors are important platelet surface receptor molecules, linked with multiple molecular gates of platelets and multiple signal channels. P2Y1 is the G-protein-coupled receptor, in which ADP is the physiological agonist; P2Y1 positively couples to phospholipase C (PLC) via Gαq, which triggers Ca^{2+} release from intracellular stores, leading to change in platelet shape and rapid, reversible platelet aggregation. Many studies have shown that functional changes corresponding ADP receptor P2Y1 gene can change the signal function of ADP, as well as decrease reactivity to aspirin, resulting in thrombotic events [1-4]. In recent years, the relevance between P2Y gene polymorphism and ischemic stroke has become a major field of research. However, studies on the relevance between P2Y1 gene polymorphism and ischemic stroke have attracted less attention. In particular, only a few studies have focused on the relevance between P2Y1 receptor and aspirin resistance (AR) orclopidogrel resistance, with inconsistent conclusions [5-9]. In the present study, we genotyped 185 cerebral infarction (CI) patients and 162 healthy people to investigate the relevance between polymorphisms of C893T gene of platelet membrane receptor P2Y1 and ischemic stroke.

Materials and methods

Study population

In the CI group, 185 CI patients, which included 105 males and 80 females, were enrolled; age 37 to 88 years with the average age of 63.72±12.27 years. All the patients are Hans of Shandong Province from the neurological ward of the affiliated hospital of Binzhou Medical College (from July 2013 to April 2014). The criteria for enrollment conformed to the diagnostic criteria of the Fourth Session of the National Conference (in China) on Cerebrovascular Disease, and confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The exclusion criteria were as follows: patients with atrial fibrillation, history of trauma surgery, diseases of the blood system, tumor, autoimmunity, and incomplete heart, lung, liver, kidney functions. The normal contrast comprised 162 individuals, including 89 males and 73 females; aged 36 to 86 years with average age of 61.89±11.74 years. All the people are healthy Hans of Shandong Province confirmed by CT or MRI. Clinical data were as follows: age, gender, smoking, drinking, systolic pressure, diastolic pressure, blood glucose, blood lipid (cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein), serum uric acid, plasma fibrinogen level, and homocysteine levels.

DNA extraction

Blood samples from a peripheral vein were obtained from each patient and healthy individual, and stored in 4 ml evacuated vacuum tubes containing 3.8% sodium citrate and ethylenediaminetetraacetic acid (EDTA), with a ratio of 1:9. The samples were then centrifuged at 3000 rpm for 10 min at room temperature. Genomic DNA was extracted from white blood cells by centrifugal column method, according to instructions of the blood genomic DNA extraction kits, which were bought from TaKaRa (Dalian Treasure Biological Engineering Co., Ltd.).

Genetic screening

We used polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis (RFLP) to detect the genotype of P2Y1 gene C893T. Primers were designed according to the search results of gene bank and the reference. The sequences of the primer for P2Y1 were as follows: Sense primer 5'-TCGAGGAGGAGAGA-ATGACC-3' and anti-sense primer 5'-TGCTGC-CATAGAGGTTCACA-3', which were composed by Shanghai Sangon Biological Engineering Co., Ltd. PCR for P2Y1 polymorphism typing was performed in a total volume of 50 μl containing 200 μmol/L of each dNTP, 10 pmol of each primer, 2 μg of DNA, 5 U of Taq DNA polymerase, and 50 μl liquid paraffin. PCR parameters consisted of initial denaturation for 5 min at 94°C, followed by 35 cycles of 55 s at 94°C for denaturation, 50 s at 54°C for annealing, and 60 s at 72°C for extension, and a final extension for 5 min at 72°C. Then, we take 5 μl PCR product for electrophoresis in 2% agarose gel (ethidium bromide was added), and 429 base pair (bp) fragment confirmed under ultraviolet light was the objective product. A 1 μl of restriction enzyme RsrII, 2 μl of 10× K Buffer, and sterile water were then added to the 5 μl PCR product to a total volume of 20 μl, which was then stored at 30°C water overnight. Then, 2 μl of 10× loading buffer was added into 20 μl PCR enzyme-digested products to terminate enzyme reaction. A 10 μl portion of PCR enzyme-digested product was then obtained for electrophoresis for 15 min in 2% agarose gel electrophoresis (ethidium bromide was added) under voltage of 110 V. Restricted DNA products were visualized by ultraviolet light and analyzed with a standard molecular weight of a 100 bp DNA ladder.

Statistical analysis

All data are presented as mean ± standard deviation (SD). The difference of measurement data between CI group and the normal contrast group was compared using T test. All SNPs evaluated in our study were tested for deviation from the Hardy-Weinberg equilibrium using the chi-square test. Genotype frequency and allele frequency between CI group and the normal contrast group were compared using χ^2 test. The relationship between the variables and CI was studied with multivariate logistic regression analysis. Statistical analysis was performed with SPSS version 19.0, and a two-tailed probability value of less than 0.05 or 0.01 was considered significant.

Table 1. Comparison of demographic characteristics and risk factors of stroke between the two groups

Category	Cerebral infarction group (n=185)	Normal contrast group (n=162)	*P value*
Age (x±SD)	63.72±12.27	61.89±11.74	0.157
Gender (M/F)	105/80	89/73	0.734
Smoking% (n)	21.6 (40)	12.3 (20)	0.023
Alcohol% (n)	16.2 (30)	10.5 (17)	0.157
Systolic pressure (mmHg)	154.86±23.88	140.15±24	<0.001
Diastolic pressure (mmHg)	88.95±14.40	82.32±12.29	<0.001
Blood glucose (mmol/L)	6.14±2.08	5.79±1.48	0.07
Cholesterol (mmol/L)	4.65±1.16	4.85±1.13	0.107
Triglyceride (mmol/L)	1.55±0.92	1.72±1.15	0.138
Low density lipoprotein (mmol/L)	2.99±0.98	3.02±0.9	0.792
High density lipoprotein (mmol/L)	1.08±0.33	1.14±0	0.079
Fibrinogen (g/L)	3.34±0.84	3.10±0.6	0.004
Serum uric acid (μmol/L)	281.56±86.56	278.40±94	0.746
Homocysteine levels (μmol/L)	17.10±12.5	14.89±9	0.069

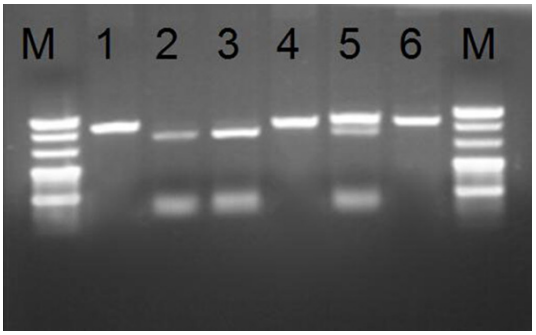

Figure 1. P2Y1 gene electrophoretogram M refers to indicator "Mark": index strip from top to bottom is 500 bp, 400 bp, 300 bp, 200 bp, and 100 bp. 1, 6 refers to PCR product: 429 bp; 2, 3 refers to 893CC: 357 bp, 72 bp; 4 refers to 893TT: 429 bp; 5 refers to 893CT: 429 bp, 357 bp, 72 bp.

Results

Clinical characteristics

The baseline characteristics of the study groups are presented in **Table 1**. No significant differences ($P>0.05$) in age, gender composition, alcohol consumption, blood glucose, cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, serum uric acid, and homocysteine were found between the two groups. However, significant differences in smoking, systolic blood pressure, diastolic blood pressure, and plasma fibrinogen level were found between the two groups ($P<0.01$ or <0.05).

Polymorphism analysis of P2Y1 gene in platelet membrane receptor

PCR enzyme-digested products are shown in **Figure 1**. The amplified fragment length of platelet membrane receptor P2Y1 gene C893T was 429 bp. The PCR product was digested with enzyme RsrII in the presence of the C allele, yielding two fragments of 357 and 72 bp for the CC genotype, three fragments of 429,357, and 72 bp in the case of the CT genotype, and a single band of 429 bp was detected for the TT genotype.

Genotype distribution

We enrolled 347 cases including 162 healthy individuals and 185 CI patients. In the CI group, 149 cases were 893CC genotype, 32 cases were 893CT genotype, and 4 cases were 893TT genotype. In the normal contrast group, 148 cases were 893 CC genotype, 13 cases were 893 CT genotype, and 1 case was 893TT genotype. The CT/TT genotype frequency (19.46%) of the CI group is obviously higher than that of the normal contrast group (8.64%), with significant difference ($X^2=8.195$, $P<0.01$). Meanwhile, the T allele frequency (10.81%) of the CI group is obviously higher than that of the normal contrast group (4.63%), with significant difference ($X^2=9.045$, $P<0.01$). The distributions of C893T gene polymorphisms of P2Y1 gene between the CI group and the normal contrast group are presented in **Table 2**.

Multivariate logistic regression analysis

Table 3 shows the results of multivariate logistic regression analysis. CI was considered the dependent variable, whereas age, gender, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, blood glucose, cholesterol, triglyceride, low-density lipo-

Table 2. Frequency comparison of C893T polymorphism of P2Y1 gene between case group and control group

Group	n	Genotype (%)				χ^2	*P*	Allele type (%)		χ^2	*P*
		CC (%)	CT (%)	TT (%)	CT/TT (%)			C (%)	T (%)		
CI group	185	149 (80.54)	32 (17.3)	4 (2.16)	36 (19.46)	8.195	0.004	330 (89.19)	40 (10.81)	9.045	0.003
Contrast Group	162	148 (91.36)	13 (8.02)	1 (0.62)	14 (8.64)			309 (95.37)	15 (4.63)		

Table 3. Multivariate logistic regression analysis with cerebral infarction as the dependent variable

Independent variable	Sig	Exp (B)	95% confidence interval of EXP (B)	
			Lower limit	Upper limit
Age	0.954	0.999	0.977	1.022
Gender	0.237	0.715	0.410	1.247
Smoking	0.243	1.576	0.734	3.385
Drinking	0.767	1.136	0.489	2.637
Systolic blood pressure	0.005	1.020	1.006	1.035
Diastolic blood pressure	0.253	1.014	0.990	1.039
Blood glucose	0.143	1.133	0.959	1.339
Cholesterol	0.362	0.839	0.576	1.223
Triglyceride	0.154	0.809	0.604	1.083
Low-density lipoprotein	0.749	1.072	0.699	1.644
High-density lipoprotein	0.278	0.633	0.277	1.447
Plasma fibrinogen level	0.022	1.480	1.059	2.069
Serum uric acid	0.749	1.000	0.997	1.002
Homocysteine level	0.286	1.012	0.990	1.034
Genotype	0.026	2.179	1.095	4.336

protein, high-density lipoprotein, serum uric acid, plasma fibrinogen level, homocysteine level, and P2Y1 C893T genotype were taken as independent variables in the analysis. Results showed that systolic blood pressure, plasma fibrinogen level, and -893T gene carriers ($P<0.05$) affect CI. After controlling for potential confounding factors, individuals who carry -893T allele had an approximately 2.179 times (OR=2.179, 95% confidence interval: 1.095-4.336, $P=0.026$) increase in the occurrence of CI compared with that of non-carriers. Therefore, the -893T allele is a risk factor for CI.

Discussion

Platelets play important roles in thrombosis after rupture of atherosclerotic plaque. Clinical research shows differences in platelet functions in different individuals; some people may have increased risk of atherosclerosis. Among the media for platelet activation, ADP is especially important because it links with the platelet surface G protein coupled P2Y receptor, and it also plays a role in the integration and cascade amplification of platelet activation and aggregation; thus, ADP is an important intermediate substance in the process of blood coagulation and thrombosis. Eight kinds of P2Y receptor subtypes had been cloned so far; among them, the P2Y1 receptor is involved in the process of information transduction of ADP. During the process, P2Y1 receptor couples with the Gq protein, combines with ADP, releases calcium, activates platelets, and changes the form of platelets, resulting in an irreversible aggregation of platelets.

The changes of the functions of ADP receptor P2Y1 gene can change the signal function of ADP and decrease the reaction to aspirin (including P2Y12 inhibitor, such as chlorine and clopidogrel), leading to the pre-thrombus state. AYSE ANIL TIMUR [10] investigated the association of P2Y1 and P2Y12 polymorphisms with on-aspirin platelet by light transmission aggregometry and TxB2 assay in 423 coronary artery disease (CAD) patients; they found that polymorphisms in P2Y1 and P2Y12 are associated with on-aspirin platelet reactivity. Hetherington SL [10] studied whether genetic variants in the P2Y1 or P2Y12 genes affect platelet response to ADP and found that a polymorphism (A1622G) in P2Y1 was associated with a significant ($P=0.007$) effect on platelet ADP response in healthy volunteers, with a greater response in carriers of the G allele (frequency=0.15). The effect was observed at all concentrations of ADP, but the greatest effect was detected at 0.1 μmol/L ADP, where the response in GG homozygotes was on average 130% higher than that seen in AA homozygotes ($P=0.006$). This genotype effect partly explains the interindividual variation in platelet response to ADP and may have clinical implications with regard to thrombotic risk. In 2012,

Lordkipanidzé M [11] included 192 Caucasian patients with stable CAD treated with daily aspirin and three years of follow-up. He found that carriers of the 1622 G/G genotype of the P2Y1 gene had significantly higher levels of arachidonic acid-induced platelet aggregation compared with non-carriers. Carrying the 1622 G/G genotype increased the risk of inadequate platelet response to aspirin, defined as arachidonic acid-induced aggregation ≥ 20%, by a factor of 8.5 (1.4-53.3, *P*=0.022); in addition, carrying the 1622 G/G genotype increased the risk of three-year major adverse cardiovascular and cerebrovascular events (MACCE) by a factor of 7 (1.4-34.7, *P*=0.017). Thus, the 1622A/G mutation of the P2Y1 gene could contribute to inadequate platelet response to aspirin and is associated with an increased risk of suffering from MACCE.

Moreover, Jefferson [12] studied 332 cases of male patients with acute myocardial infarction and found a close relation between AR and the C893T polymorphism of P2Y1 gene. Patients with heterozygous C893T allele that show AR are approximately three times higher than that of allele carriers with common homozygous C893; the mechanism remains unclear. However, some studies have found the opposite result. Lev EI [8] reported that the change of P2Y1 gene polymorphism 1622A>G do not cause the increase of AR. StoreyRF [13] also found that single nucleotide polymorphisms (SNPs) in P2RY1 do not significantly influence inhibition of ADP-induced platelet aggregation by ticagrelor in Caucasian patients. Kunicki TJ [14] studied the effect of prophylactic aspirin (ASA) ingestion on platelet function in 463 patients with stroke, transient ischemic attack (TIA), or acute coronary disease (ACD). He correlated ASA responsiveness with haplotypes of seven candidate genes, which were selected for their documented role in platelet function, namely, the genes for integrins alpha 2, beta1, and alpha IIbbeta3 (ITGA2, ITGA2B, and ITGB3), platelet glycoproteins Ibalpha and VI (GPIBA and GP6), the purinergic receptor P2Y1 (P2RY1), and prostaglandin H synthase 1 (PTGS1=COX1). However, ASA responsiveness was not associated with haplotypes of any of the seven candidate genes. Kim KA [15] analyzed the P2Y1 (1622A>G) and P2Y12 (139C>T, 744T>C, ins801, 52G>T, 34C>T) polymorphisms in 158 Korean healthy participants using pyrosequencing methods to evaluate the allele frequencies of P2Y1 and P2Y12 genetic polymorphisms in Korean population and to assess their role in ADP (5 μmol/L)-induced maximal platelet aggregation; results showed that the P2Y1 and P2Y12 genes are very polymorphic in Korean population, and maximal platelet aggregation in response to ADP is associated with the P2Y12 52 G>T polymorphism, but not with the P2Y1 1622 A>G polymorphism.

In China, Wang L [16] reported that on the C893T site of the P2Y1 gene, the frequency of P2Y1 (893 C>T) in AR group and aspirin semi-responder group is significantly higher than that in aspirin-sensitive group. This finding indicates that if P2Y1 gene 893Tis present instead of 893C, the mutation leads to a remarkable increase of patients with AR; however, ifP2Y1 gene 1622G is present instead of 1622A, the mutation does not lead to a significant influence in AR of patients. Ye Pei [17] studied 330 cases of patients (above 40 years old) with coronary heart disease, hypertension, CI, and with or without type 2 diabetes mellitus, and found that a T for C base substitution at position 893 of P2Y1 gene was associated with increased AR (OR=3.16, 95% confidence interval 1.36-7.16, *P*=0.04); therefore, patients with this mutation have a high probability of occurrence of AR. By contrast, the 1622 A>G site is asynonymous mutation, and thus the mutation could be conserved without changing the amino acid sequence; no significant difference in protein expression between the wild type and mutant type, which may be the reason for no significant correlation between 1622 A>G variation of P2Y1 gene and AR [18].

The above studies on the relationship between the platelet P2Y1 receptor gene and thrombotic disease mainly focus on the correlation of aspirin and other drugs; however, studies on platelet receptor P2Y1 gene polymorphism as an independent factor for ischemic stroke are still lacking. Thus, the role of platelet receptor P2Y1 gene in ischemic stroke should be studied further.

The present study showed that age, gender composition, alcohol consumption, blood glucose, cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, cholesterol, serum uric acid, and homocysteine level were not significantly different (*P*>0.05) between the

CI group and the normal contrast group, whereas smoking, systolic blood pressure, diastolic blood pressure, and plasma fibrinogen level showed significant differences ($P<0.01$ or <0.05). We performed statistical analysis of the combined TT gene and TC gene group, given the low number of the TT gene group. In the CI group, CT/TT genotype frequency is 19.46%, which is significantly higher ($X^2=8.195$, $P<0.01$) than that of the normal contrast group (i.e., 8.64%). The T allele frequency is 10.81%, which is significantly higher ($X^2=9.045$, $P<0.01$) than that of the normal contrast group (i.e., 4.63%). By adjusting for age, gender, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, blood glucose, cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, serum uric acid, plasma fibrinogen level, and homocysteine level, and taking healthy control group as reference, multivariate logistic regression analysis showed that individuals who carry -893T allele had an approximately 2.179 times (OR=2.179, 95% confidence interval: 1.095-4.336, $P=0.026$) increase in the occurrence of CI compared with that of non-carriers. Therefore, we infer that the P2Y1 gene C893T polymorphism of the platelet membrane receptor is correlated with ischemic stroke. The P2Y1 gene 893CT/TT genotype may be one of the risk factors of stroke, and the allele T may be the etiological factor of ischemic stroke. In addition, the small sample size in this study may have low representation of the populations and differences in genetic factors exist in different populations; therefore, differences in research results may be obtained. Ischemic stroke is a multi-gene disease caused by the combined effects of multiple genetic factors and environmental factors; therefore, better conclusions may be obtained by developing more selective gene loci polymorphism tests and conducting comprehensive analysis with large sample sizes, considering many factors and indexes.

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Disclosure of conflict of interest

None.

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