

Original Article

Association between *COL1A2* gene polymorphisms and susceptibility to the intracerebral hemorrhage in a Chinese population

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Abstract: We firstly conducted a study to investigate the role of three common SNPs (rs42524 in exon 28, rs1800238 in exon 32, and rs2621215 in intron 46) in the susceptibility to intracerebral hemorrhage. A total 286 patients with proven intracerebral hemorrhage and 355 control subjects were consecutively recruited between May 2012 and October 2014. The DNA was extracted from venous blood samples using the TIANamp Blood DNA Kit (Tiangen Biotech, Beijing, China). Genotyping of *COL1A2* rs42524, rs1800238, and rs2621215 was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). We found that the frequencies of the GG, GC and CC genotypes of *COL1A2* rs42524 were significantly different between patients with intracerebral hemorrhage and controls ($\chi^2 = 18.49$, $P < 0.001$). By unconditional logistic regression analysis, the GC and CC genotypes of *COL1A2* rs42524 was associated with an increased risk of intracerebral hemorrhage when compared to the GG genotype, and the adjusted ORs (95% CI) of the GC and CC genotypes were 2.15 (1.03-4.48) and 3.00 (1.51-5.98), respectively. Moreover, the GC + CC genotype of *COL1A2* rs42524 was correlated with a higher risk of intracerebral hemorrhage, compared to the wide-type genotype (Adjusted OR = 1.67, 95% CI = 1.14-2.43). In addition, individuals carrying the TT genotype of *COL1A2* rs1800238 had a higher risk of developing intracerebral hemorrhage when compared with the GG genotype (Adjusted OR = 2.68, 95% CI = 1.17-6.12). However, the *COL1A2* rs2621215 polymorphism was not significantly associated with increased risk of intracerebral hemorrhage. We observed a significant interaction between *COL1A2* rs42524 and hypertension in the risk of intracerebral hemorrhage (Correlation coefficient = 0.087; $P = 0.02$). In conclusion, our study suggests that *COL1A2* rs42524 and 1800238 polymorphisms contribute to the development of intracerebral hemorrhage.

Keywords: *COL1A2*, intracerebral hemorrhage, Chinese population

Introduction

Stroke is a leading cause of death and disability worldwide, including China. It is estimated that the number of patients who die from stroke is three times higher than the number that die from coronary heart disease in China and is two to three times higher than the number of stroke-related deaths in Western nations [1]. In China, it is estimated that there are about 2 million people who have experienced their first stroke, and there are more than one million stroke-related deaths annually in China [2]. About 50% of strokes are caused by intracerebral hemorrhage [3]. The etiology of this disease is not well

understood, although it is associated with many lifestyle and environmental factors, such as age, hypertension, diabetes, hyperlipidemia, smoking, drinking, obesity high salt dietary [4, 5]. However, not all individuals with the related risk factors would develop intracerebral hemorrhage, which suggests that many hereditary factors may contribute to the risk of this disease. Identification of genetic polymorphisms associated with intracerebral hemorrhage would illuminate its underlying biology.

Type I collagen is responsible for maintaining vessel wall elasticity, and it is a necessary part of the extracellular matrix [6]. Type I collagen is

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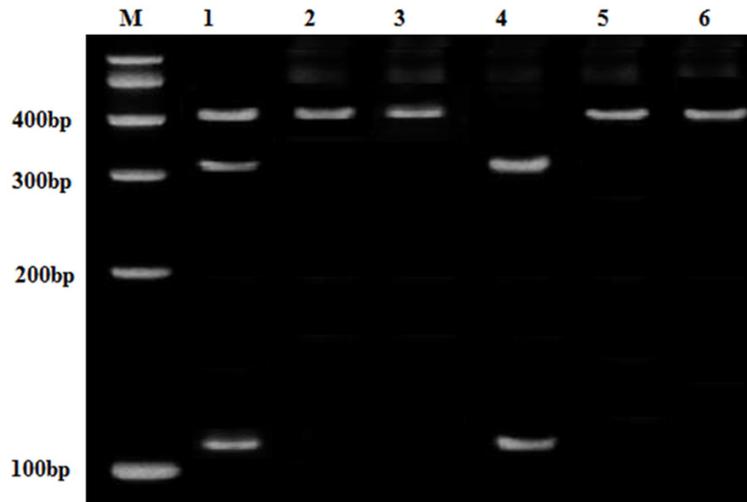


Figure 1. Agarose gel electrophoresis images for *COL1A2* rs42524. 1 lane: GC genotype; 2, 3 and 6 lanes: CC genotype; 4 and 5 lane: GG genotype.

transcribed by the *COL1A1* and *COL1A2* genes, respectively. The *COL1A2* gene is located at chromosome 7q22.1 and this gene encodes the pro- α 2 chain protein. The *COL1A2* polymorphism causes an amino acid substitution, and thus alters the integrity of type I collagen, and it plays an important role in reducing vessel wall rigidity and inducing the destruction of blood vessel walls [7]. Several studies have reported the role of *COL1A2* polymorphisms and development of cardiovascular disease [7-10]. However, few studies reported the association between *COL1A2* polymorphisms and risk of intracerebral hemorrhage [11-13]. In this study, we firstly conducted a study to investigate the role of three common SNPs (rs42524 in exon 28, rs1800238 in exon 32, and rs2621215 in intron 46) in the susceptibility to intracerebral hemorrhage.

Material and methods

Subjects

A total of 286 patients with proven intracerebral hemorrhage were consecutively recruited from Xinxiang Central Hospital between May 2012 and October 2014. Intracerebral hemorrhage was diagnosed by brain computed tomography (CT) or brain magnetic resonance imaging (MRI) scans. The diagnosis of intracerebral hemorrhage was according to the criteria from the fourth National Cerebrovascular Academic Conference in 1995. Patients who

had intracerebral hemorrhage caused by arteritis, trauma, drugs, tumor, cerebral vascular malformation, or aneurysm were excluded from this study.

Control groups included 355 subjects who obtained the regular medical check-up at our hospital between May 2012 and October 2014. All the control subjects underwent brain computed tomography and/or brain magnetic resonance imaging testing and were confirmed to be lack of intracerebral hemorrhage, and they are free of malignant tumor, and serious kidney and

liver diseases. Between all intracerebral hemorrhage patients and control subjects gave a signed written informed consent before enrolment into the study. The ethics committee of our hospital approved the study protocols.

The demographic, lifestyle and clinical characteristics of patients with intracerebral hemorrhage and control subjects were collected from a structured questionnaire and/or medical records. The demographic and lifestyle data included sex, age, body mass index (BMI), tobacco smoking, alcohol drinking, hypertension and diabetes. The body mass index was calculated using the formula $BMI = \text{Weight}/(\text{Height})^2$. Venous blood samples were obtained after 12 hours fasting period from antecubital vein to assess the triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

DNA extraction and genotyping

The DNA was extracted from venous blood samples using the TIANamp Blood DNA Kit (Tiangen Biotech, Beijing, China). Genotyping of *COL1A2* rs42524, rs1800238, and rs2621215 was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Primer sequences for the *COL1A2* rs42524, rs1800238, and rs2621215 were designed using MassARRAY Assay Design 3.1 software (SEQUENOM, San Diego, CA, USA).

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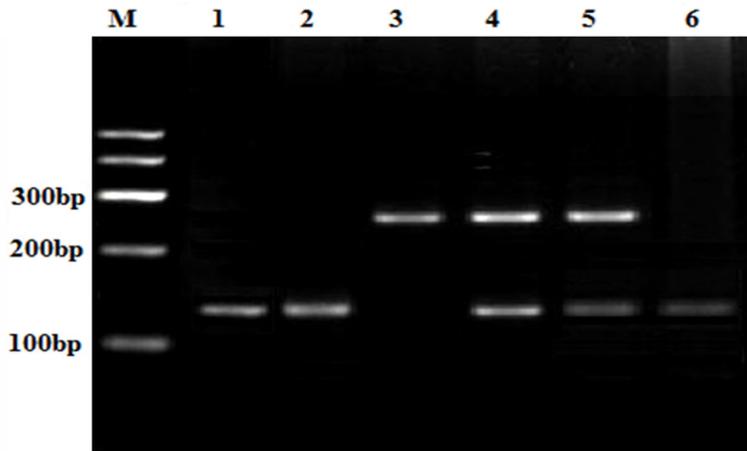


Figure 2. Agarose gel electrophoresis images for *COL1A2* rs1800238. 1, 2 and 6 lanes: GG genotype; 4 and 5 lanes: GT genotype; 3 lane: TT genotype.

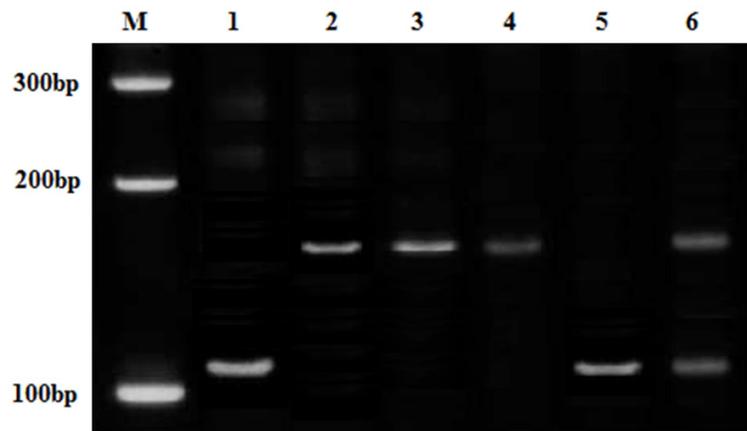


Figure 3. Agarose gel electrophoresis images for *COL1A2* rs2621215. 1 and 5 lanes: GG genotype; 2-4 lanes: TT genotype; 6 lane: GT genotype.

The PCR fragments of the investigated polymorphisms were subsequently digested with their specific restriction enzyme. The genotype results of *COL1A2* rs42524, rs1800238, and rs2621215 were shown in **Figures 1-3**. The PCR reaction conditions were as follows: 94°C for 4 min; 35 cycles of 94°C for 30 s, 60°C for 30 s, and 72°C for 30 s; and 72°C for 7 min. Digestion products were separated by electrophoresis on ethidium bromide stained agarose gel and visualized under UV light.

Statistical methods

All statistical analysis was conducted using the SPSS statistical package software, version 17.0 (SPSS Inc, Chicago, IL, USA). The demo-

graphic, lifestyle and genotype frequencies between the two groups were compared using the Chi-square (χ^2)-test or student T test. Whether the *COL1A2* rs42524, rs1800238, and rs2621215 deviated from the Hardy-Weinberg equilibrium (HWE) was examined using a χ^2 test with one degree of freedom. Multiple logistic regression models were established to assess the association between *COL1A2* rs42524, rs1800238, and rs2621215 polymorphisms and development of intracerebral hemorrhage, and the results were expressed using Odds ratios (ORs) and 95% confidence intervals (CIs). All tests were two-sided with a significant level of *P*-value < 0.05.

Results

The demographic and clinical characteristics of patients with intracerebral hemorrhage and control subjects are summarized in **Table 1**. No significant difference was found between the patients and control subjects in terms of alcohol drinking ($\chi^2 = 1.21$, *P* = 0.27) and HDL-c (*t* = 0.63,

P = 0.26). Patients with intracerebral hemorrhage would be more likely to be males ($\chi^2 = 8.19$, *P* = 0.004), have higher age (*t* = 6.21, *P* < 0.001) and BMI (*t* = 8.52, *P* < 0.001), have a habit of tobacco smoking ($\chi^2 = 8.59$, *P* = 0.003), be suffered from diabetes mellitus ($\chi^2 = 28.45$, *P* < 0.001) and hypertension ($\chi^2 = 12.12$, *P* < 0.001), and have higher triglyceride (*t* = 4.77, *P* = 0.002) and higher LDL-c (*t* = 3.00, *P* = 0.001).

We found that the frequencies of the GG, GC and CC genotypes of *COL1A2* rs42524 were significantly different between patients with intracerebral hemorrhage and controls ($\chi^2 = 18.49$, *P* < 0.001) (**Table 2**). The genotype distributions of the *COL1A2* rs42524 (*P* = 0.07) and rs2621215 (*P* = 0.50) polymorphism were

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Table 1. Demographic, lifestyle and clinical characteristics of study subjects

Characteristics	Patients n = 286	%	Controls n = 355	%	t- or χ^2 -test	P-value
Age (years)	60.41 ± 10.60		55.61 ± 8.97		6.21	< 0.001
Sex						
Female	104	36.36	169	47.61		
Male	182	63.64	186	52.39	8.19	0.004
BMI (kg/m ²)	24.76 ± 2.31		23.27 ± 2.11		8.52	< 0.001
Tobacco smoking						
No	151	52.80	228	64.23		
Yes	135	47.20	127	35.77	8.59	0.003
Alcohol drinking						
No	179	62.59	237	66.76		
Yes	107	37.41	118	33.24	1.21	0.27
Diabetes mellitus						
No	210	73.43	318	89.58		
Yes	76	26.57	37	10.42	28.45	< 0.001
Hypertension						
No	186	65.03	275	77.46		
Yes	100	34.97	80	22.54	12.12	< 0.001
Triglyceride (mmol/L)	1.84 ± 1.24		1.45 ± 0.82		4.77	< 0.001
Total cholesterol (mmol/L)	4.51 ± 0.87		4.58 ± 0.89		1.00	0.16
HDL-c (mmol/L)	1.42 ± 0.70		1.43 ± 0.77		0.17	0.43
LDL-c (mmol/L)	3.47 ± 1.16		3.21 ± 1.03		3.00	0.001

Table 2. Genotype frequencies of COL1A2 rs42524, rs1800238, and rs2621215 between intracerebral hemorrhage patients and control subjects

COL1A2	Patients N = 286	%	Controls N = 355	%	χ^2 test	P value	P for HWE		
							In controls	In database	In controls
Rs42524									
GG	167	58.39	246	69.30					
GC	80	27.97	93	26.20					
CC	39	13.64	16	4.51	18.49	< 0.001	0.07	0.1783	0.1761
Rs1800238									
GG	229	80.07	298	83.94					
GT	37	12.94	44	12.39					
TT	20	6.99	13	3.66	3.74	0.15	< 0.001	0.0992	0.0986
Rs2621215									
TT	139	48.60	190	53.52					
GT	114	39.86	136	38.31					
GG	33	11.54	29	8.17	2.70	0.26	0.50	0.2278	0.2732

in line with the Hardy-Weinberg equilibrium in the control group, while the genotype frequencies of rs1800238 were not ($P < 0.001$). Moreover, the minor allele frequencies of COL1A2 rs42524, rs1800238, and rs2621215 were consistent with those in the dbSNP database of the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/snp/>).

By unconditional logistic regression analysis, the GC and CC genotypes of COL1A2 rs42524 was associated with an increased risk of intracerebral hemorrhage when compared to the GG genotype, and the adjusted ORs (95% CI) of the GC and CC genotypes were 2.15 (1.03-4.48) and 3.00 (1.51-5.98), respectively (Table 3). Moreover, we found that the GC + CC geno-

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Table 3. Association between *COL1A2* rs42524, rs1800238, and rs2621215 and risk of intracerebral hemorrhage

<i>COL1A2</i>	Patients N = 286	%	Controls N = 355	%	Crude OR (95% CI)	P value	Adjusted OR (95% CI) ¹	P value
Rs42524								
GG	167	58.39	246	69.30	Ref.		Ref.	
GC	80	27.97	93	26.20	1.27 (0.79-2.02)	0.30	2.15 (1.03-4.48)	0.04
CC	39	13.64	16	4.51	3.64 (1.62-8.60)	0.001	3.00 (1.51-5.98)	0.002
GC + CC	119	41.61	109	30.70	1.60 (1.05-2.46)	0.02	1.67 (1.14-2.43)	0.008
Rs1800238								
GG	229	80.07	298	83.94	Ref.		Ref.	
GT	37	12.94	44	12.39	1.10 (0.58-2.06)	0.74	2.33 (0.90-6.03)	0.08
TT	20	6.99	13	3.66	2.67 (0.94-8.18)	0.04	2.68 (1.17-6.12)	0.02
GT + TT	57	19.93	57	16.06	1.39 (0.81-2.39)	0.20	1.48 (0.92-2.37)	0.10
Rs2621215								
TT	139	48.60	190	53.52	Ref.		Ref.	
GT	114	39.86	136	38.31	1.14 (0.74-1.77)	0.53	1.06 (0.56-1.99)	0.86
GG	33	11.54	29	8.17	1.54 (0.74-3.17)	0.21	1.37 (0.74-2.52)	0.32
GT + GG	147	51.40	165	46.48	1.21 (0.81-1.83)	0.33	1.31 (0.91-1.87)	0.15

¹Adjusted for sex, age, BMI, tobacco smoking, diabetes mellitus, hypertension, triglyceride and LDL-c.

Table 4. Interaction between *COL1A2* rs42524 and rs1800238 and risk of intracerebral hemorrhage based on the potential confounding factors

Variables	Correlation coefficient	P value	Correlation coefficient	P value
Sex	0.031	0.44	0.01	0.77
Age	0.032	0.42	0.01	0.75
BMI	0.036	0.36	0.003	0.95
Tobacco smoking	0.072	0.07	0.01	0.74
Diabetes mellitus	0.058	0.14	0.05	0.18
Hypertension	0.087	0.02	0.009	0.82
Triglyceride	0.021	0.59	0.01	0.80
LDL-c	0.044	0.27	0.07	0.06

type of *COL1A2* rs42524 was correlated with a higher risk of intracerebral hemorrhage, compared to the wide-type genotype (Adjusted OR = 1.67, 95% CI = 1.14-2.43). In addition, individuals carrying the TT genotype of *COL1A2* rs1800238 had a higher risk of developing intracerebral hemorrhage when compared with the GG genotype (Adjusted OR = 2.68, 95% CI = 1.17-6.12). However, the *COL1A2* rs2621215 polymorphisms were not significantly associated with an increased risk of intracerebral hemorrhage.

We further analyze the association between *COL1A2* rs42524 and rs1800238 and risk of

intracerebral hemorrhage based on the sex, age, BMI, tobacco smoking, diabetes mellitus, triglyceride and LDL-c ($P > 0.05$; **Table 4**). We observed a significant interaction between *COL1A2* rs42524 and hypertension in the risk of intracerebral hemorrhage (Correlation coefficient = 0.087; $P = 0.02$).

Discussion

Polymorphisms can have an effect on gene expression and contribute to differences between individuals in susceptibility to and severity of disease. Intracerebral hemorrhage is generally believed to be a disease influenced by interactions between genes and the environment, resulting in high mortality and disability. However, the etiology of intracerebral hemorrhage is unclear; many recent studies have reported that molecular factors may play an important role in the development of the disease. In our study, we firstly conducted a case-control study to investigate the role of *COL1A2* rs42524, rs1800238, and rs2621215 in the risk of intracerebral hemorrhage in a Chinese population. We found that the *COL1A2* rs42524 and rs1800238 polymorphisms were significantly associated with increased risk of intracerebral hemorrhage in a Chinese population.

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Type I collagen is the most abundant collagen of vertebrate connective tissue, and is also found in vessels [14]. Type I collagen is an important structural component of broad tissues, and many physiological functions have been found in it, including specific interactions with various molecules and cells. Amino acid substitution could change the structural stability of the *COL1A2* rs42524, rs1800238, and rs2621215 variants, and thus influence the protein expression and functions. Previous study has reported that the *COL1A2* plays an important role in the expression of collagen type I in vivo and human tissue repair and development [15], and also contributes to the development, stabilization, maturation and remodeling of blood vessels [16-18]. We observed an significant interaction between *COL1A2* rs42524 and hypertension, suggesting *COL1A2* rs42524 may increase the risk of intracerebral hemorrhage through influencing the blood pressure.

Currently, only three studies reported the association between *COL1A2* gene polymorphisms and development of intracerebral hemorrhage, but the results are inconclusive [11-13]. Liu et al. conducted a study with 393 Chinese patients with primary intracerebral hemorrhage and 486 controls, and they found that the *COL1A2* rs42524 polymorphism could be a genetic risk factor for primary intracerebral hemorrhage in a Chinese population [11]. Another study also reported that the rs42524 polymorphism of *COL1A2* could be a genetic risk factor for sporadic intracranial aneurysms [13]. However, another study in a Korean population, and Joo et al. reported that rs2621215 in the *COL1A2* was marginally associated with an increased risk of intracerebral hemorrhage, but the rs42524 polymorphism showed no associated with an increased risk of this disease [12]. In our study, we found that *COL1A2* rs42524 and rs1800238 polymorphisms contributed to the development of intracerebral hemorrhage, but the rs2621215 polymorphism did not. The discrepancies of the above mentioned studies may be due to differences in ethnicities, selection of patients and controls, and/or sample size.

Our study had three major limitations. First, the patients with intracerebral hemorrhage and control subjects were selected from a single

hospital, resulting in a selection bias; that is, these subjects may not be representative of other populations. Second, some gene-gene interaction may be considered in the risk of intracerebral hemorrhage. Third, the sample size of this study was relatively small, which may not represent the general population and could limit the statistical power to find differences between groups.

In conclusion, our study suggests that the *COL1A2* rs42524 and rs1800238 polymorphisms contribute to the development of intracerebral hemorrhage, but the rs2621215 polymorphism does not. Further studies with large sample size are greatly required to confirm the results of our findings.

Disclosure of conflict of interest

None.

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