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Is Alpha-1 Antichymotrypsin Gene Polymorphism a Risk Factor for Primary Intracerebral Hemorrhage? A Case-Control Study and Meta-Analysis

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Alpha-1 antichymotrypsin (ACT) signal peptide A/T polymorphism has been suggested to play a role in various brain diseases with arterial wall pathology. We conducted a case-control study and a meta-analysis to evaluate the association between this polymorphism and risk of primary intracerebral hemorrhage.

Material/Methods: A total of 188 patients and 200 age- and sex-matched healthy controls were enrolled in our case-control study. The ACT polymorphism was genotyped by PCR-LDR. Further meta-analysis was conducted by searching literature from PUBMED, EMBASE, and Chinese National Knowledge Infrastructure databases until December 2014, then combining data using STATA10.0.

Results: Similar genotype distribution was detected between PICH patients and healthy controls (p=0.523). Further analysis based on hypertension and location of hemorrhage did not observe significant association. Multiple logistic regression analysis also failed to identify ACT polymorphism as an independent risk factor for PICH. With regard to meta-analysis, a total of 6 case-control studies including 932 PICH patients and 1140 controls were enrolled. Pooled ORs failed to detect a significant association of ACT signal peptide A/T polymorphism with PICH (dominant model: OR=1.03, 95%CI=0.72–1.46; recessive model: OR=1.08, 95%CI=0.88–1.32). Subgroup analysis based on hypertension revealed no association in hypertensive PICH or in normotensive PICH.

Conclusions: Our case-control study in a Chinese population did not detect a significant association between ACT signal peptide A/T polymorphism and PICH. Moreover, meta-analysis combining data from relevant studies failed to provide evidence for the association. Further well-designed studies with larger sample sizes are warranted to verify our findings.

MeSH Keywords: alpha 1-Antichymotrypsin • Cerebral Hemorrhage • Polymorphism, Single Nucleotide

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Background

Primary intracerebral hemorrhage (PICH) accounts for 10–15% of all cases of stroke and is a devastating disease with high mortality and morbidity rates [1,2]. It occurs with an annual incidence of 10 to 20 cases per 100 000 people and increases with age [3]. Various risk factors have been identified to contribute to ICH, such as hypertension, age, alcohol consumption, drug abuse, and cerebral amyloid angiopathy (CAA) [4]. Recently, genetic factors have been implicated in the susceptibility to PICH.

Alpha-1 antichymotrypsin (ACT) is an acute-phase plasma protein produced mainly by hepatocytes [5]. It functions as a serine proteinase inhibitor (serpin) of several proteases, such as cathepsin G [6]. The neutrophil-released cathepsin G could promote platelet aggregation, which results in coagulation disorder [7]. Furthermore, as a proteolytic enzyme, cathepsin G may lead to the degradation of extracellular matrix [7]. Therefore, ACT might play a role in the pathophysiology of intracerebral hemorrhage through regulating the activity of cathepsin G.

The ACT gene (also named *SERPINA3*) was mapped on chromosome 14q32.1 [8]. A common polymorphism has been identified in the exon II of ACT gene (rs4934), resulting in the amino acid substitution from $^{-15}$Ala to $^{-15}$Thr in the signal peptide [9]. The variant genotype (T/T+A/T) has been associated with increased expression level of plasma ACT [10]. Genetic epidemiological studies have implicated this polymorphism as risk factor for Alzheimer disease, Parkinson disease, and multiple system atrophy [11–14]. The role of ACT polymorphism in the development of PICH has also been evaluated in several studies, but the results remain controversial. Obach et al. confirmed the association between the ACT-TT genotype and development of hemorrhagic stroke in a study enrolling 99 ICH patients and 80 asymptomatic controls [15]. Fu et al. reported increased risk of ICH in a Chinese population carrying with ACT-AT or TT genotypes [16]. However, these findings failed to be replicated by other studies [17–20]. The inconsistency might be attributed to the small sample size and the subsequent insufficient statistical power, different ethnic background, or even the potential existence of selection bias.

We conducted a case-control study to explore the association between polymorphism of ACT gene and the susceptibility to hemorrhagic stroke in a Chinese population. Moreover, we performed a meta-analysis to combine our findings with those from available studies on the same topic.

Material and Methods

Study subjects

This was a population-based case-control study. The study protocol was approved by the ethics committee of West China Hospital of Sichuan University. Written informed consents were obtained from all study subjects.

Consecutive adult patients admitted to our hospital with a diagnosis of PICH were enrolled in this study from November 2011 to September 2012. The diagnosis of ICH was confirmed by brain CT in all cases. Patients were excluded if the ICH was due to trauma, brain tumors, arteriovenous malformation, aneurysm, hemorrhagic transformation of cerebral infarction, and hemorrhagic diatheses due to coagulopathy or anticoagulant therapy, as well as those with severe renal or liver disease. Age- and sex-matched healthy controls without history of hemorrhagic stroke were also enrolled in this study.

Medical records of each patient were reviewed and the following baseline characteristics were collected: age, sex, hypertension (defined as pre-hemorrhage blood pressure documented to be >140 mmHg systolic or >90 mmHg diastolic, or use of anti-hypertensive agent), diabetes mellitus (previous diagnosis of diabetes or was using insulin or an oral hypoglycemic agent), hyperlipidemia (previous diagnosis or was using statin), alcohol consumption (>300 g/week), and smoking (>10 cigarettes/day). Location of hemorrhage was classified as lobar or deep (basal ganglia, thalamus, brain stem, and cerebellum) hemorrhage.

Genotyping

Genomic DNA was extracted from the peripheral blood using the DNA Blood Kit (Bioteke Corp., China) according to the manufacturer's instructions. The ACT polymorphism was genotyped by the PCR-LDR sequencing method, as reported previously [21]. The PCR primers used were 5'-CCATCTGGCCCTCTGAGACTT-3' (forward) and 5'-GTTGGCGGAGGCTAATCCGAG-3' (reverse). PCR reactions were carried out in an ABI 9700 device (Applied Biosystems, USA) in a 15-µl volume containing 1.5 µl 10×PCR buffer, 15 ng of genomic DNA, 3 pmol of each primer, 0.2 mM of dNTP, 1.5 U of Taq polymerase (MBI Fermentas), and 2.5 mM of MgCl2. After a 5-min initial denaturation step at 95°C, 35 cycles of PCR reaction consisting of 94 °C15s, 55°C 15 s, and 72°C 30 s were performed, followed by a 10-min final extension step at 72°C in a thermal cycler. Ligase detection reaction [22] was performed in a total volume of 10 µl containing 3 µl PCR product, 1 µl 10×Taq DNA ligase buffer, 2 U of Taq DNA ligase (NEB), and 0.1 pmol of each probe. LDR probes were 1 common probe and 2 discriminating probes. The LDR parameters were as follows: 95°C for 2 min, 35 cycles of 94°C

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Table 1. Demographic data in patients with primary intracerebral hemorrhage (PICH) and controls.

Characteristics	PICH patients (n=188)	Controls (n=200)	*p*
Age, y	57.8±14.0	56.4±9.6	0.282
Sex, male/female	132/56	136/64	0.637
Hypertension, n (%)	98 (52.1%)	60 (30.0%)	<0.0001
Diabetes mellitus, n (%)	16 (8.5%)	8 (4.0%)	0.065
Hyperlipidemia, n (%)	5 (2.7%)	2 (1.0%)	0.271
Smoking, n (%)	63 (33.5%)	40 (20.0%)	0.003
Drinking, n (%)	38 (20.2%)	30 (15.0%)	0.177

for 30 s, and 60°C for 2 min. The fluorescent products of LDR were differentiated by ABI 3730xl (Applied Biosystems, USA). For quality control, the genotyping analysis was done blind as regards the subjects. Randomly selected PCR-amplified DNA fragments (about 5% of the samples) were also examined by DNA sequencing to check the validity of the genotyping, and the results were 100% concordant.

Statistical analysis

Demographic data was compared in the PICH patients and healthy controls using t test or χ^2 as appropriate. Hardy-Weinberg equilibrium in the control population was tested by a goodness-of-fit chi-squared test. Genotype distribution and allele frequency in PICH patients and controls were analyzed by χ^2 test. The role of ACT polymorphism in PICH (lobar, deep, hypertensive, and normotensive) was evaluated by multiple regression analysis. The calculations were performed using SPSS for Windows (Version 18.0; SPSS Inc., Chicago, IL, USA). Power calculations were performed with Quanto 1.2.4 (*http://hydra.usc.edu/GxE/*). A *p* value of <0.05 was considered significant.

Meta-analysis

Studies for meta-analysis were identified by extended computer-based search of PubMed, Embase, and China National Knowledge Infrastructure (CNKI) databases, with the last search update in December 2014. The search strategy was based on combinations of: "SERPINA3,""α1-antichymotrypsin,""ACT,""polymorphism(s)," "variant(s),""mutation(s),""intracerebral hemorrhage," and "hemorrhagic stroke". Cited references from selected articles and relevant reviews were also screened to identify additional eligible studies. Retrieved publications that examined the association of ACT polymorphism with PICH were subsequently assessed in their entirety for inclusion in the meta-analysis. Studies were eligible if they had determined the distribution of alleles and/or genotypes for the ACT gene polymorphism in unrelated cases with PICH and in unrelated controls without PICH. Family-based studies were not considered. When studies with overlapping subjects were considered eligible, we only included the one with the larger number of patients. The corresponding author was contacted if the data regarding genotype distribution was insufficient. We only used data from full-published papers rather than that from conference abstracts, case reports, or review articles. The following information was extracted from each included study: first author's name, publication year, country, mean age, male percentage, number of cases and controls, source of control, matching criteria, and genotype distribution.

Genotype distribution in the control group was checked in each study for departure from Hardy-Weinberg equilibrium (HWE) using the chi-squared goodness-of-fit test. The strength of the association between ACT polymorphism and PICH susceptibility was estimated using ORs and their corresponding 95% confidence interval (CI).The pooled ORs were performed for co-dominant model (T/T *vs.* A/A, A/T *vs.* A/A), dominant model (T/T+A/T *vs.* A/A), and recessive model (T/T *vs.* A/T+A/A).

Cochran's *Q* test and the I^2 statistic were used to measure heterogeneity across the included studies. A *P* value of more than 0.05 for the *Q* test indicated a lack of heterogeneity, and the fixed-effects model (the Mantel–Haenszel method) was subsequently used to calculate the summary OR [23]. Otherwise, the random-effects model (the DerSimonian and Laird method) was applied [24]. Sensitivity analysis was performed to test the robustness of the findings by: 1) omitting studies with controls not in accordance with HWE; and 2) sequentially omitting individual studies. Publication bias was estimated by visually assessing the asymmetry of Begg's funnel plot. Furthermore, Egger's test was performed to provide quantitative evidence for checking of publication bias.

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Table 2. Genotype and allele distribution of ACT signal peptide A/T polymorphism.

	AA	AT	TT	χ^2	*p*	T
Control	42 (21.0%)	96 (48.0%)	62 (31.0%)			220 (55.0%)
PICH	31 (16.5%)	96 (51.1%)	61 (32.4%)	1.296	0.523	218 (58.0%)
Hypertensive	19 (19.4%)	50 (51.0%)	29 (29.6%)	0.249	0.883	108 (55.1%)
Normotensive	12 (13.3%)	46 (51.1%)	32 (35.6%)	2.479	0.289	110 (61.1%)
Lobar	8 (16.7%)	22 (45.8%)	18 (37.5%)	0.906	0.636	58 (60.4%)
Deep	23 (16.4%)	74 (52.9%)	43 (30.7%)	1.291	0.524	160 (57.1%)

Table 3. Logistic regression analysis for different genetic models.

	Allele		Dominant model		Recessive model	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
PICH	1.17 (0.87–1.57)	0.305	1.47 (0.86–2.51)	0.160	1.10 (0.70–1.72)	0.675
Hypertensive	1.22 (0.76–1.95)	0.414	1.60 (0.72–3.56)	0.246	0.94 (0.55–1.58)	0.804
Normotensive	1.20 (0.81–1.78)	0.371	1.60 (0.75–3.43)	0.227	1.14 (0.64–2.05)	0.655
Lobar ICH	1.24 (0.78–1.99)	0.359	1.37 (0.58–3.24)	0.479	1.31 (0.66–2.58)	0.438
Deep ICH	1.07 (0.78–1.49)	0.665	1.39 (0.77–2.52)	0.272	0.95 (0.58–1.55)	0.825

Dominant model, T/T+A/T *vs.* A/A; Recessive model, T/T *vs.* A/T+A/A.

Results

Case-control study

A total of 188 patients and 200 healthy controls were enrolled in this study. The demographic data is summarized in Table 1. Mean age was 57.8±14.0 years for patients with PICH, and 56.4±9.6 years for healthy controls. Frequency of hypertension, diabetes, and smoking was significantly higher in ICH patients than in controls.

Genotype distribution in the controls was in accordance with HWE (p=0.668). There was no significant difference regarding the genotype distribution or T allele frequency between the PICH patients and healthy controls (Table 2). Furthermore, when compared with controls, no significant difference was detected in hypertensive PICH, normotensive PICH, lobar ICH, or deep ICH. Allele frequencies, dominant model (T/T+A/T *vs.* A/A), and recessive model (T/T *vs.* A/T+A/A) were examined using multiple logistic regression analysis after adjusted age, sex, hypertension, diabetes, hyperlipidemia, smoking, and alcohol consumption. We failed to identify ACT polymorphism as independent risk factor for PICH (Table 3).

Meta-analysis

After a comprehensive literature search and records screening, full texts of 7 studies were considered for further evaluation. The studies by Vila et al. [19] and Misra et al. [25] were then excluded. Patients in Vila [19] et al. were in duplicate with Obach et al. [15], and the latter study enrolled more patients. Misra et al. [25] enrolled both patients with recurrent intracerebral hemorrhage and those with non-recurrent hemorrhage. Patients enrolled seemed in duplicate with Somarajan et al. [18]. Moreover, fewer patients were enrolled when compared with Somarajan [18]. Therefore, a total of 6 case-control studies including 932 PICH patients and 1140 controls were enrolled (data from our study also included). Characteristics of the included studies are summarized in Table 4. All studies except Fu et al. provided separate data in hypertensive ICH patients and normotensive ICH patients. With regard to location of hemorrhage, only Dardiotis et al. [17], Pera et al. [20], and our study provided separate data. Therefore, subgroup analysis was only performed based on blood pressure. Overall, we did not observe an association between ACT polymorphism and PICH (Table 5 and Figure 1). In the subgroup analysis, however, we still failed to observe an association of ACT polymorphism with hypertensive PICH, or normotensive PICH. Sensitivity analysis was

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Table 4. Characteristics of studies included in the meta-analysis.

Author	Year	Country	Ethnicity	ICH type	Case/control	Genotyping method	Matching criteria	HWE
Dardiotis	2008	Greece	Caucasian	PICH	147/206	PCR-RFLP	Age, sex	Yes
Fu	2002	China	Asian	PICH	220/276	PCR-RFLP	NA	No
Obach	2001	Spain	Caucasian	PICH	99/80	PCR-RFLP	Geographic area	Yes
Pera	2006	Poland	Caucasian	PICH	95/190	PCR-RFLP	Age, sex	Yes
Somarajan	2010	India	Asian	PSICH	183/188	PCR-RFLP	NA	Yes
Our study	2013	China	Asian	PICH	188/200	PCR-LDR	Age, sex	Yes

PICH – primary intracerebral hemorrhage; PSICH – primary spontaneous intracerebral hemorrhage; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR – polymerase chain reaction-ligase detection reaction; NA – not available; HWE – Hardy-Weinberg equilibrium.

Table 5. Meta-analysis of ACT signal peptide A/T polymorphism on primary intracerebral hemorrhage risk.

	N	Case/ control	Allele		Dominant model		Recessive model	
			OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h
PICH	6	932/1140	1.04 (0.92–1.18)	0.052	1.03 (0.72–1.46)	0.014	1.08 (0.88–1.32)	0.069
Hypertensive	5	416/864	0.91 (0.77–1.08)	0.772	0.80 (0.61–1.04)	0.803	1.00 (0.75–1.32)	0.500
Normotensive	5	296/864	1.05 (0.86–1.28)	0.101	1.01 (0.74–1.39)	0.223	1.22 (0.66–2.27)	0.019

Dominant model, T/T+A/T *vs.* A/A; Recessive model, T/T *vs.* A/T+A/A; P_h, *P* value for heterogeneity.

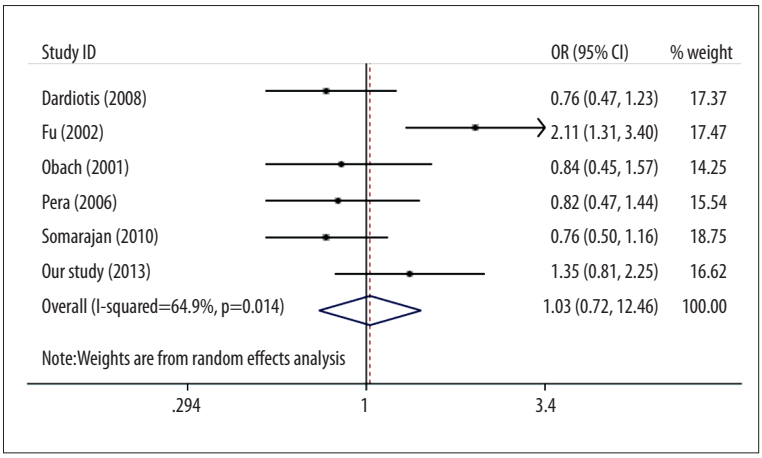

Figure 1. Forest plot for association of ACT signal peptide A/T polymorphism with the risk of primary ICH (T/T+A/T *vs.* A/A). The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares indicates the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95%CI.

performed by omitting each study in turn and by omitting the study that was not in accordance with HWE (Fu et al. [16]), and the results did not change. Publication bias was not detected in Begg's funnel plot (Figure 2) or Egger's test (data not shown).

Discussion

By investigating 188 PICH patients and 200 age- and sex-matched healthy controls, no association was detected between ACT polymorphism and PICH development. In the present case-control study, the power was greater than 0.80 to detect positive association with disease allele frequency of 0.55 under a dominant model, assuming the odds ratio of 2.80 reported in the study of Obach et al. [15].

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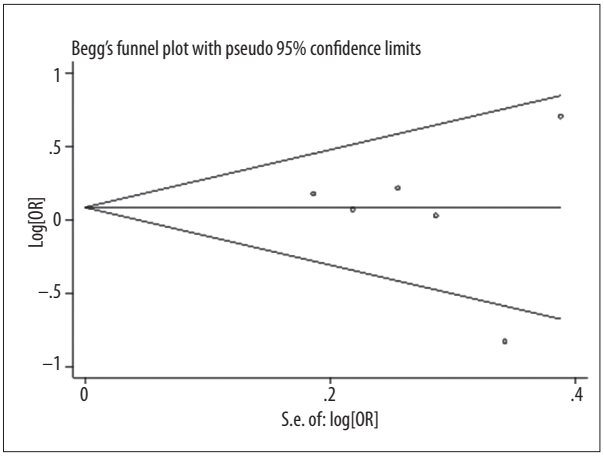

Figure 2. Begg's funnel plot for publication bias test (T/T *vs.* A/T+A/A). Each point represents a separate study for the indicated association. Log[OR]: natural logarithm of OR. Horizontal line: mean effect size.

Our results were in agreement with studies in Greek [17], Polish [20], and Indian [18] populations. Obach et al. [15] first reported the association between ACT T/T genotype and hemorrhagic stroke in a Spanish population (OR 2.80, 95%CI 1.19–6.58). However, when stratified based on hypertension, a positive association was only detected in normotensive ICH (OR 3.10, 95%CI 1.10–8.68) but not in hypertensive ICH (OR 2.20, 95%CI 0.88–5.47). Neither normotensive nor hypertensive ICH was found to be associated with ACT polymorphism in our study. Ethnic and environmental differences might partially account for this difference. The frequency of T/T genotype in the control group in our study was 31%, higher than that in Obach et al. (15%). On the other hand, the normotensive ICH group only included 33 patients in the study by Obach et al. Therefore, it might also be possible that the association was due to chance. Interestingly, Fu et al. reported a significant association of ACT variant carrier (A/T+T/T) with risk of hypertensive ICH but not normotensive ICH [16]. When focusing on lobar ICH and deep ICH separately, we did not observe significant findings, which is consistent with previous studies [17,20].

It has been suggested that proteolytic enzymes may play a role in the pathogenesis of ICH [26]. As a serine proteinase inhibitor, ACT could regulate the activity of serine proteinases, including neutrophil cathepsin G, which could result in the degradation of vascular matrix proteins and coagulation factors [27]. Therefore, it was hypothesized that ACT polymorphism might be associated with the development of ICH. However, results addressing this issue were conflicting; our study detected a negative association. We then performed a meta-analysis to combine our findings with all available data from eligible published studies concerning the role of ACT polymorphism in the development of PICH. Pooled ORs did not support the hypothesis in overall comparison or stratified analysis based on hypertension. Therefore, we supposed that ACT signal peptide A/T polymorphism might have a significant but slight effect on PICH or even play no role in the pathogenesis of PICH. Further well-designed studies with larger sample sizes in different population are warranted to validate our findings. We could not exclude the existence of linkage disequilibrium of this polymorphism with another functional mutation(s) of the ACT gene [20].

Several limitations in our study should be addressed. Firstly, the level of statistical significance was not Bonferroni-corrected. However, the association would remain negative after being Bonferroni corrected since no positive association was observed. Secondly, since patients admitted in our hospital and enrolled in this study would be those who survived the onset of ICH, survival bias might exist. Furthermore, as the largest teaching hospital in southwest China, patients with more serious conditions tend to be admitted in our hospital, which might also lead to the introduction of selection bias. Thirdly, since detailed information on the identified risk factor for PICH was not supplied by studies included in our meta-analysis, only crude odds ratios were pooled for the association between ACT polymorphism and PICH risk.

Conclusions

Our case-control study in a Chinese population did not detect a significant association between ACT signal peptide A/T polymorphism and PICH. Moreover, our meta-analysis of relevant studies failed to provide evidence for the association.

Conflict of interest

The authors have declared no conflicts of interest.

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