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Association between the *FGB* gene polymorphism and ischemic stroke: a meta-analysis

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ABSTRACT. To clarify the relationship between the β-fibrinogen (*FGB*) genetic polymorphism (-148C>T) and ischemic stroke, we identified studies by searching PubMed, EMBASE, and the Chinese National Knowledge Infrastructure (CKNI) databases. Data from eligible studies were extracted and subjected to meta-analysis. Publication bias was tested using a funnel plot. We identified 12 independent case-control studies containing 1536 ischemic stroke patients and 1329 control subjects. Our results showed that the -148C>T polymorphism in the *FGB* gene was associated with an increased risk of ischemic stroke [CC *vs* (TT+CT), odds ratio = 0.69, 95% confidence interval (CI) = 0.59-0.80, P < 0.0001; TT *vs* (CC+CT), odds ratio = 3.01, 95%CI = 1.29-7.05; P = 0.01; T *vs* C, odds ratio = 1.32, 95%CI = 1.15-1.52, P < 0.0001] by a meta-analysis. The results of our meta-analysis suggested that the -148C>T polymorphism in the *FGB* gene is a susceptibility marker of ischemic stroke.

Key words: β-fibrinogen; Ischemic stroke; Meta-analysis

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INTRODUCTION

China is the world's most populous country, in which stroke is an enormous health care burden. Approximately 2 million people are affected by ischemic stroke each year in China (WHO, 2000). Previous studies suggested that the plasma fibrinogen level is associated with ischemic stroke risk (Wilhelmsen et al., 1984; Maresca et al., 1999). Fibrinogen is encoded by 3 separate genes located in a 50-kb cluster on the long arm of chromosome 4, which encodes for the α, β, and γ chains (Kant et al., 1985). The rate-limiting step in fibrinogen formation is the synthesis of the β-polypeptide chain regulated by a β-fibrinogen promoter (Roy et al., 1990). Polymorphisms in the β-fibrinogen gene (*FGB*), including the β -148C>T polymorphism, have been shown to be related to elevated plasma fibrinogen levels (Guo et al., 2009; Yuan et al., 2010). Previous studies suggested that the *FGB* -148C>T polymorphism is associated with an increased risk of ischemic stroke in the Chinese population (Fu et al., 2005, 2006; Chen et al., 2007). However, each study included a relatively small sample size, which may lack sufficient power for detecting the slight effects of the -148C>T polymorphism on stroke. Meta-analysis may provide more credible evidence by systematically summarizing existing data. In the present study, we collected all published case-control studies to determine the relationship between the -148C>T polymorphism and stroke to perform a meta-analysis and to clarify the relationship between the *FGB* gene -148C>T polymorphism and ischemic stroke.

MATERIAL AND METHODS

Literature search and selection

A publication search was carried out in PubMed, EMBASE, and the Chinese National Knowledge Infrastructure (CNKI) using the following search terms: ("fibrinogen" or "β-fibrinogen" or "*FGB*") and ("cerebral infarction" or "stroke" or "brain infarction" or "cerebrovascular disease") and ("SNP" or "polymorphism" or "mutation" or "genetics"). Publication language was restricted to English and Chinese, and the subjects were limited to Chinese in our search. Using an online retrieval and literature review, references obtained from the databases were reviewed again to ensure that no relevant studies were missed.

Selection criteria

Inclusion criteria were as follows: a) independently published case-control or cohort studies examining the relationship between *FGB* polymorphism and stroke; b) with comprehensive direct or indirect statistical indicators: odds ratio (OR) or relative risk values and 95% confidence interval (95%CI); and c) similar themes and methods, such as case-control or cohort studies examining the relationship between the *FGB* gene polymorphism and stroke. The studies were excluded if relevant data were not available or if there was heterogeneity in the gene polymorphisms in the control population. For the heterogeneity test method, the Q-test and the I^2 test included in the RevMan 5.2 software were used.

Data extraction

The research design, enrolled patients, observation results of the literature, and se-

lected trials were evaluated by the author. The Cochrane Handbook 5.2 quality evaluation criteria was used to assess the methodological quality of the studies such as study included subjects and impact factors, the source of the cases and controls, matching, age, and gender. To determine data quality by the quality of the determined literature, duplicate studies, those with poor quality or little information, and those including special selection for laboratory samples were excluded; relevant data were extracted from the studies included.

Statistical analysis

For each study, we first examined whether the genotype distribution in controls was consistent with Hardy-Weinberg equilibrium using the χ^2 test. Meta-analysis was performed using the RevMan 5.2 software provided by the Cochrane Collaboration. The Q-test and the I^2 test were used to examine the heterogeneity between each study. Using the heterogeneity test, if $P > 0.05$, the fixed-effect model was selected, and if $P < 0.05$, the random-effect model was selected to merge the OR values. $P < 0.05$ was considered to be significant. Analysis of sensitivity included the difference of point estimations and confidence intervals of the combined effect values of different models to observe whether it changed the result; poor-quality studies were excluded or reanalyzed according to the quality evaluation criteria to determine whether it changed the findings. To test for publication bias, the RevMan 5.2 statistical software was used to construct a funnel plot.

RESULTS

Literature search

A total of 313 studies were preliminarily detected, and 301 studies were excluded because of duplicate publication and nonclinical-based research literature. Twelve studies (LV et al., 2003; Liu et al., 2004; Qian et al., 2004; Pan et al., 2005; Song et al., 2005; Xu et al., 2005; Ma et al., 2006; Fu et al., 2006; Song et al., 2006; Lu et al., 2007; Liu and Zhao, 2008; Yuan et al., 2010) met the inclusion criteria and were included in the present study.

Study characteristics

The characteristics of the studies included are summarized in Table 1. The 12 studies included a total of 1536 ischemic stroke cases and 1329 control subjects. All subjects included in these studies were of Chinese descent. A classic polymerase chain reaction assay was performed in all studies. The genotyping method in all studies was polymerase chain reaction-restriction fragment length polymorphism, and the genotype distributions among the controls of all studies were in agreement with Hardy-Weinberg equilibrium.

Meta-analysis

The association between the -148C>T polymorphism and susceptibility to stroke was analyzed in 12 independent studies with 1536 stroke patients and 1329 control subjects. The results of the meta-analysis are shown in Figures 1, 2, and 3. These 3 figures indicate the correlation between ischemic stroke and the *FGB* -148C>T polymorphism in the 12 case-control studies.

Table 1. Characteristics of the studies included.

Author	Year	Country	Genotyping methods	Groups	No.	-148C>T (N)		
						CC	CT	TT
Fu Y	2006	China	PCR-RFLP	Case	132	75	50	7
				Control	171	102	58	11
Liu CF	2004	China	PCR-RFLP	Case	90	43	39	8
				Control	102	64	34	4
Liu Z	2008	China	PCR-RFLP	Case	220	105	85	30
				Control	140	84	49	7
Lu SJ	2007	China	PCR-RFLP	Case	148	72	63	13
				Control	130	79	45	6
Lv B	2003	China	PCR-RFLP	Case	151	70	65	16
				Control	113	62	47	4
Ma AJ	2006	China	PCR-RFLP	Case	151	85	63	3
				Control	101	70	30	1
Pan XD	2005	China	PCR-RFLP	Case	69	41	26	2
				Control	60	41	18	1
Qian JJ	2004	China	PCR-RFLP	Case	102	66	30	6
				Control	90	43	39	8
Song YQ	2005	China	PCR-RFLP	Case	88	38	42	8
				Control	80	47	27	6
Song YQ	2006	China	PCR-RFLP	Case	135	53	56	26
				Control	120	65	43	11
Xu F	2005	China	PCR-RFLP	Case	90	52	32	6
				Control	60	47	17	2
Yuan XD	2010	China	PCR-RFLP	Case	160	101	47	12
				Control	162	112	42	8

The heterogeneity test of the various studies revealed heterogeneous results ($P = 0.04$, $I^2 = 45\%$; $P < 0.01$, $I^2 = 86\%$; $P = 0.14$, $I^2 = 31\%$); therefore, the fixed-effect or the random-effect models were used for analysis. Overall, the association between the *FGB* -148TT/CT genotype and higher risk of ischemic stroke was observed in the recessive model (OR = 0.69, 95%CI = 0.59-0.80; $P < 0.0001$; Figure 1) and in the dominant model (OR = 3.01, 95%CI = 1.29-7.05; $P = 0.01$; Figure 2). Additionally, the -148 T allele carriers were found to be associated with an increased risk of ischemic stroke (OR = 1.32, 95%CI = 1.15-1.52; $P < 0.0001$; Figure 3).

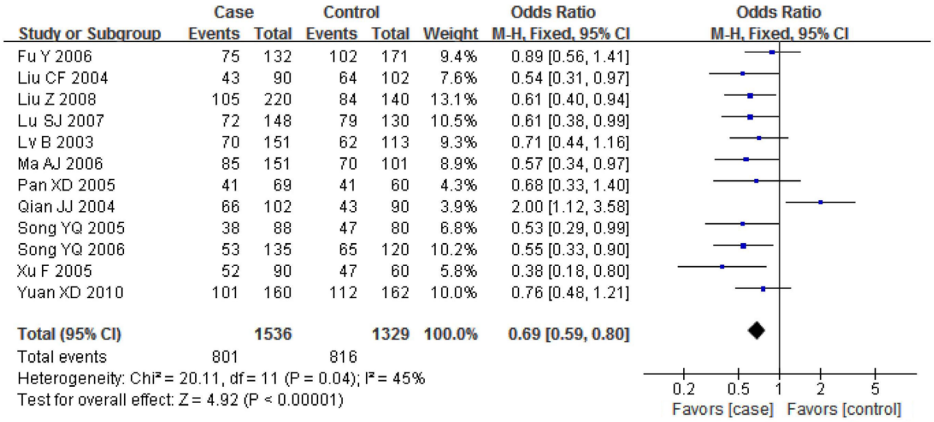

Figure 1. Forest plot of stroke and the -148C>T polymorphism (CC vs TT+CT). The horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI.

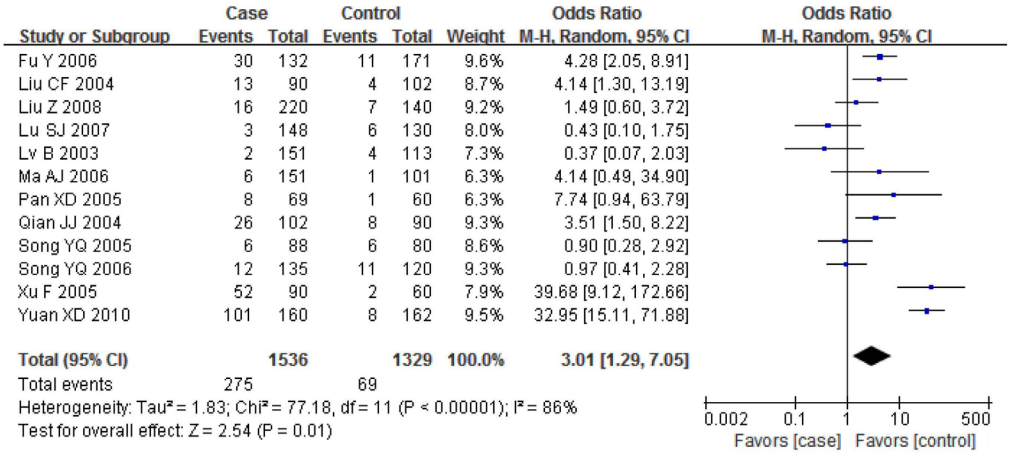

Figure 2. Forest plot of stroke and the -148C>T polymorphism (TT *vs* CC+CT). The horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI.

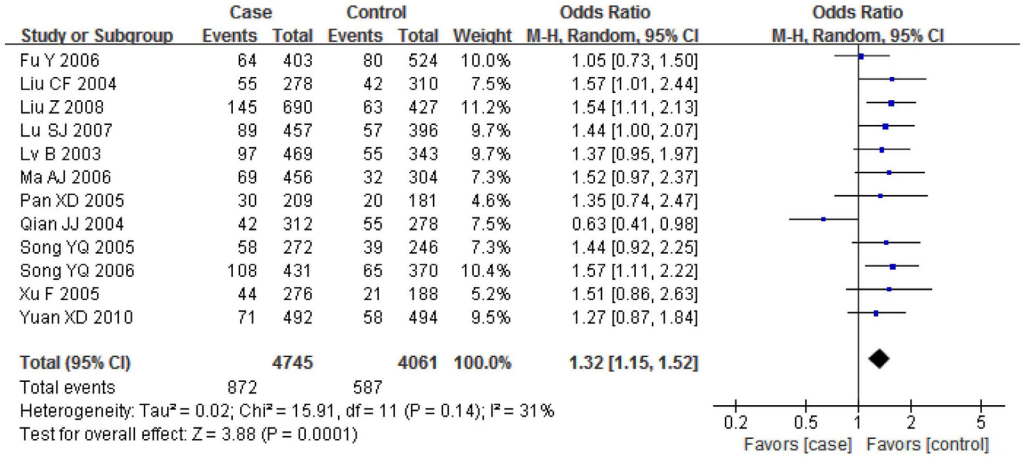

Figure 3. Forest plot of stroke and the -148 C>T polymorphism (T *vs* C). The horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI. In this analysis, the fixed-effect model was used.

Publication bias

The RevMan 5.2 software was used to analyze publication bias; the funnel plot (Figure 4) showed that the points were evenly distributed and symmetrical, and most points were within the 95%CI. The shape of the funnel plots showed no clear asymmetry compared to the Egger test and no statistical evidence of bias. These results indicate that there was no publication bias and that the results of the study were credible.

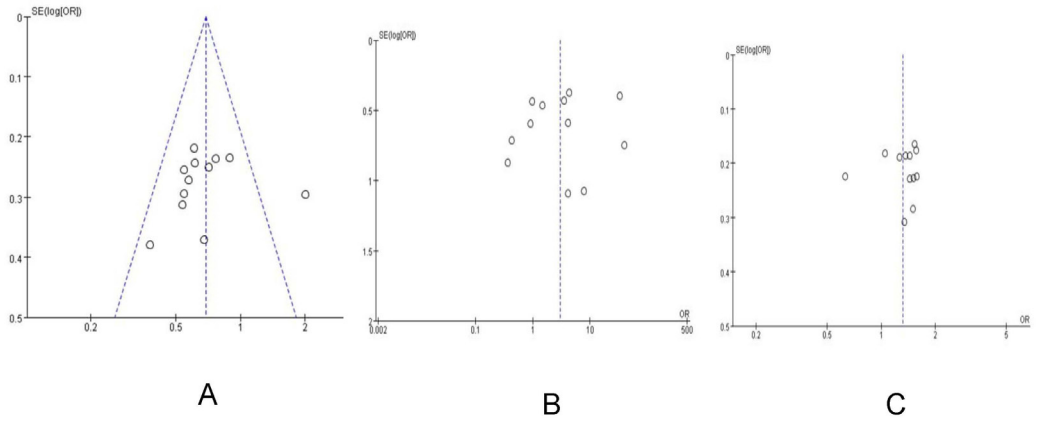

Figure 4. Begg's funnel plot for publication bias tests. Each point represents a separate study for the indicated association. Log OR represents natural logarithm of OR. Vertical line represents the mean effect size. **A.** CC *vs* (TT+CT); **B.** TT *vs* (CC+CT); **C.** T *vs* C.

DISCUSSION

In the present study, we found that the -148C>T polymorphism in the *FGB* gene was significantly associated with ischemic stroke in a Chinese population using a meta-analysis. Meta-analysis combines comparable studies to increase the sample size and statistical power, drawing a more compelling result. In the present study, no publication bias was observed, all subjects were Chinese, and the genotypes in all studies were detected using genetic DNA from blood samples with the polymerase chain reaction-restriction fragment length polymorphism genotyping method. Genotypes in all studies were evaluated for quality control. Genotype distribution of controls in all studies was consistent with Hardy-Weinberg equilibrium. Polymorphisms in *FGB*, particularly those involved in the rate-limiting steps of β-chain formation, have been shown to be closely related to elevated plasma fibrinogen level and ischemic stroke (Zhang et al., 2003; Zhao et al., 2003). In the present study, the results of 12 studies were combined to analyze the relationship between the -148C>T polymorphism and ischemic stroke. The results showed that there was a 32% increased risk of stroke in patients with the T allele compared with the wild-type C allele. Thus, the T allele may be a genetic risk factor that increases the susceptibility to stroke at protein and genetic levels.

However, there were some limitations to this meta-analysis. Although the genotyping methods used in all studies were the same, other clinical factors such as age, gender, and different therapies in each study may lead to bias. Determining whether these factors influence the results requires further investigation.

In conclusion, our study suggested that the -148C>T polymorphism in the *FGB* gene was associated with a significantly increased risk of ischemic stroke in the Chinese population.

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