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Three polymorphisms of ALOX5AP and risk of ischemic stroke in Chinese: Evidence from a meta-analysis

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ABSTRACT

The impacts of three polymorphisms (SG13S114A/T, SG13S89A/G and SG13S32A/C) of 5-lipoxygenase activating protein (ALOX5AP) on the risk of ischemic stroke (IS) have been extensively studied for Chinese people, while conflicting results have been reported. The aim of meta-analysis was to further explore the associations to get a more robust conclusion. We researched the databases of Medline, Embase and Wangfang with latest update of August 1st, 2013. Odds ratio and corresponding 95% confidence interval (OR and 95%CI) were used to present the strength of the associations. Eleven case–control studies with 11,037 Chinese peoples (5361 IS cases and 5676 controls) were included. Overall, combined analysis indicated that AA genotype of ALOX5AP SG13S114A/T was significantly associated with increased risk of IS incidence compared with TT genotype [OR and 95%CI: 1.47 (1.13–1.91), $P = 0.005$]. In addition, when subgroup analysis was conducted by subtypes of IS (atherothrombotic- or small artery disease-IS, AHS- or SAD-IS), A allele of SG13S114A/T was found to be associated with increased risk of AHS-IS compared with T allele [OR and 95%CI: 1.51 (1.28–1.79), $P < 0.01$ for AA vs. TT, and 1.12 (1.03–1.22), $P = 0.010$ for A carriers v. T carriers]. However, SG13S89A/G and SG13S32A/C were not overall associated with IS incidence. Due to limited number of included studies, subgroup analyses were not conducted for SG13S89A/G and SG13S32A/C polymorphisms. Sensitivity analyses indicated the robustness of all combined analyses, and publication bias was not found. In conclusion, ALOX5AP SG13S114A/T, rather SG13S89A/G and SG13S32A/C, was significantly associated with risk of IS development for Chinese. More studies were required to warrant the findings of this study.

1. Introduction

Stroke is one of the most common diseases in the world, and notably causes high mortality and disability. For instance, stroke is the third leading cause of death in the United States. More than 700,000 new cases of IS are diagnosed per year, and there are more than 4.4 million stroke survivors [1]. In addition, about 2.5 million new cases of stroke are diagnosed per year in China, and there are more than 7.5 million stroke survivors [2]. Ischemic stroke (IS) as the main subtype of stroke accounts for over 50% of all stroke cases. The incidence of IS is a complex process with multiple factors involved, including environmental and genetic factors. It has been confirmed that smoking and drinking are important risk factors for IS incidence [3,4]. On the other hand, numerous genetic polymorphisms have been found to be contributors of IS incidence, including 5-lipoxygenase activating protein (ALOX5AP) gene.

It has been reported that 5-lipoxygenase (5-LO) regulated by membrane protein 5-lipoxygenase-activating protein (FLAP) is a key enzyme for metabolizing the oxidation of arachidonic acid (AA) to leukotriene A4 (LTA4) in the leukotriene pathway [5], which is significantly associated with atherosclerotic vascular pathological diseases like IS and myocardial infarction. Three single-nucleotide polymorphisms (SG13S114A/T, SG13S89A/G and SG13S32A/C) of ALOX5AP with the relationship to IS incidence have been extensively studied in Asians and Caucasians; however, conflicting results have been reported. A case–control study conducted by Kaushal R [6] based on 357 White and Black patients of IS and 482 controls implicated that none of the three ALOX5AP single-nucleotide polymorphisms (SNPs) were associated with risk of IS development. However, another study conducted by Lohmussaar E et al. [7] based on 639 European stroke patients and 736 healthy controls found that SG13S114A/T, but not SG13S89A/G and SG13S32A/C, was associated with risk of IS incidence. Similarly, a case–control and meta-analysis including 1092 IS patients and 781 healthy controls of two different subsets from Spain and Portugal and including published case–control studies [8] also found that SG13S114A/T was a risk factor for IS development.

Different ethnic peoples with the same genetic polymorphism may have different magnitudes of susceptibilities to the same diseases. Taking AGT M235T polymorphism as an example, a recent meta-analysis based on 17 case–control studies indicated that it was associated with risk of IS incidence in Asians rather than in Caucasians.

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Table 1
The basic information of included studies in this meta-analysis.

Authors	Year	Cases	Controls	SG13S114A/T			SG13S89A/T			SG13S32A/C		
				Case: MAF[a]	Control: MAF	HWE[b]	Case: MAF[a]	Control: MAF	HWE[b]	Case: MAF[a]	Control: MAF	HWE[b]
Zhang	2006	1285	1713	0.30	0.30	0.08	0.05	0.05	0.15	–	–	–
Gao	2008	100	100	0.30	0.29	0.77	0.05	0.06	0.18	–	–	–
He	2009	412	368	0.39	0.34	0.05	–	–	–	–	–	–
Xu	2009	472	312	0.31	0.29	0.72	0.04	0.05	0.14	0.38	0.32	<0.01
Gao	2010	346	425	0.80	0.63	0.01	0.03	0.02	0.69	0.26	0.33	0.37
Lee	2011	291	279	0.42	0.41	0.85						
Zhao	2012	682	598	0.33	0.29	0.99	0.05	0.05	0.06	0.41	0.40	<0.01
Zhang	2012	236	218	0.36	0.38	0.79	0.02	0.02	0.76	0.40	0.34	0.33
Wang	2012	690	767	0.38	0.36	0.95	–	–	–	–	–	–
Sun	2012	440	486	0.36	0.28	0.74	–	–	–	0.31	0.31	0.72
Li	2013	411	411	0.41	0.36	0.40	–	–	–	–	–	–

[a] MAF, minor allele frequency; for SG13S114A/T, MAF is A allele for SG13S89A/T, MAF is A allele; for SG13S32A/C, MAF is C allele.
[b] HWE, Hardy–Weinberg equilibrium.

In this meta-analysis, we explored the associations of three SNPs of ALOX5AP (SG13S114A/T, SG13S89A/G and SG13S32A/C) with the risk of IS. In order to get a more robust conclusion, we restricted the participants of this study within Chinese peoples.

2. Materials and methods

2.1. Literature search

We electronically searched the potential eligible articles in English and Chinese published in the following databases: (i) Medline in PubMed searching engine; (2) Embase database; (3) Wangfang Chinese database, and (4) Chinese National Knowledge Infrastructure (CNKI) database. The latest date for searching literatures was August 1st, 2013. The keywords for literature searching were: '5-lipoxygenase activating protein' or 'ALOX5AP', 'polymorphism' or 'variant' or 'genotype', and 'ischemic stroke' or 'brain infarction' or 'cerebral infarction'. The searching was conducted with restriction on human subjects, and references of included studies were reviewed to find additional eligible studies for this meta-analysis.

2.2. Selection criteria

All included studies must meet the following criteria: (1) case–control study explored the association between ALOX5AP SG13S114A/T, SG13S89A/G and SG13S32A/C polymorphisms and risk of IS in Chinese peoples; and (2) provided the sufficient data for combined analyses. If there were more than two studies using the same or overlapped data, the study providing more information for combined analysis was prior to be selected.

2.3. Data extraction

The data in included studies were extracted by two authors (Ye F and Liu NN) independently. Disagreements were solved with all authors together to get a consensus. The following data were extracted: the name of first author, publication year, number of IS cases and controls, minor allele frequency (MAF) in case and control groups, subtype of IS and the testing result of Hardy–Weinberg equilibrium (HWE). According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [9], IS consists of atherothrombotic-IS (AHS), small artery disease-IS (SAD) and cardioembolic-IS subtypes.

2.4. Statistical methods

The combined OR and 95%CI were calculated for the genetic comparisons to illustrate the strength of the associations between three SNPs of ALOX5AP and risk of IS, and P value of Z-test <0.05 indicated the statistical significance. Subgroup analyses for subtype of IS (AHS- or SAD-IS) were conducted for ALOX5AP SG13S114A/T

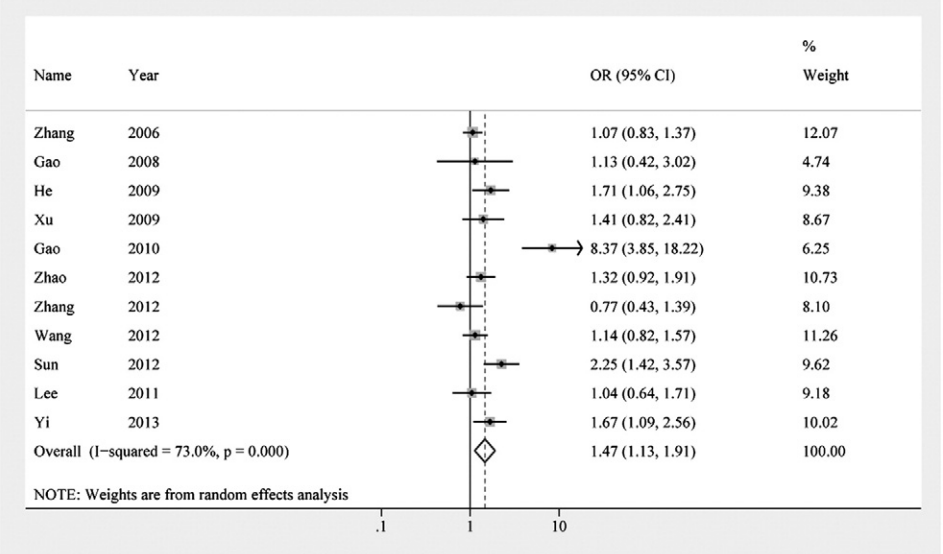

Fig. 1. Combined analysis indicated that AA genotype of ALOX5AP SG13S114A/T was significantly associated with increased risk of IS for Chinese compared with TT genotype. Because of between-study heterogeneity, random-effect model was used.