

## Meta-Analysis

# ALOX5AP rs10507391 polymorphism and the risk of ischemic stroke in Caucasians: an update meta-analysis

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Received August 21, 2017; Accepted October 25, 2017; Published October 31, 2017

Doi: <http://dx.doi.org/10.14715/cmb/2017.63.10.22>

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**Abstract:** Some reports evaluated the association between ALOX5AP rs10507391 polymorphism and the risk of ischemic stroke in Caucasians. The results remained unknown. Thus, we did a meta-analysis to evaluate this association. Nine case-control studies with 4198 patients and 3699 controls were included in this meta-analysis. A significant association was found between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in Caucasians (OR=1.18; 95%CI, 1.08–1.28;  $P=0.0002$ ). ALOX5AP rs10507391 polymorphism was associated with ischemic stroke risk in Caucasians from Europe (OR=1.20; 95%CI, 1.09–1.32;  $P=0.0002$ ) but not from other countries (OR=1.13; 95%CI, 0.95–1.36;  $P=0.17$ ). No significant association was found between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in males (OR=1.12; 95%CI, 0.91–1.39;  $P=0.28$ ). Moreover, ALOX5AP rs10507391 polymorphism was not associated with cardioembolic ischemic stroke risk (OR=1.04; 95%CI, 0.73–1.48;  $P=0.84$ ). In conclusion, this study found that ALOX5AP rs10507391 polymorphism was associated with ischemic stroke risk in Caucasians.

**Key words:** ALOX5AP; Ischemic stroke; Genetic; Polymorphism.

## Introduction

Ischemic stroke is the rapid development of a focal neurologic deficit caused by a disruption of blood supply to the corresponding area of brain (1). An increasing number of patients have had access to therapy over recent years due to improvements in pre- and intra-hospital systems (2). Early detection of the atheromatous changes in the carotid artery will reduce the stroke related morbidity and mortality. Although stroke has been believed to be a multifactorial disorder with minimal classical patterns of inheritance, accumulating evidence has shown the importance of genetic factors (3).

ALOX5-activating protein (ALOX5AP) initialize the biosynthesis of leukotrienes (LTs) from arachidonic acid (AA) (4). LTs initiate leukocyte activation and promote the adhesion of monocytes on the vascular wall, a process that plays an important role in the pathogenesis of atherosclerosis and inflammatory diseases, including ischemic stroke (5). Elias et al. found that ALOX5 and ALOX5AP expression is increased in humans and rodents with obesity and insulin resistance (6). Some reports evaluated the association between ALOX5AP rs10507391 polymorphism and the risk of ischemic stroke in Caucasians (7-14). The results remained unknown. Thus, we did a meta-analysis to evaluate this association.

## Materials and Methods

### Publications search

The electronic databases PubMed, Embase, and Web of Science (ISI) were searched using the following terms: “ischemic stroke” in combination with “ALOX5AP” and “polymorphism or variant or mutation”. Additional studies not captured by our database searches were identified through reviewing the reference lists of retrieved articles.

### Inclusion and exclusion criteria

All selected studies complied with the following criteria: (1) case-control study; (2) about the association between ALOX5AP rs10507391 polymorphism and the risk of ischemic stroke in Caucasians; and (3) had available genotype frequencies of cases and controls or could be calculated from the paper. Accordingly, the exclusion criteria were (1) duplicate data, (2) abstract, reviews, and animal studies.

### Data extraction

Two authors extracted the data from included studies independently. The following data were collected from each study: the first author, year, country, ethnicity, sample size, age, female, and subtype of ischemic stroke.

### Statistical analysis

The strength of the associations between the

**Table 1.** Characteristics of included studies.

Author	Year	Country	Ethnicity	Sample size	Age	Female (%)	Subtype of IS
Meschia	2005	USA	Caucasian	270/206	64.8 ± 15.0	47	NA
Lohmussaar	2005	European	Caucasian	639/736	65 ± 18.2	37	NA
Zee	2006	USA	Caucasian	259/600	61.0 ± 0.3	0	NA
Kaushal	2007	USA	Caucasian	241/221	69	53	Cardioembolic
Domingues-Montanari 1	2010	Spain	Caucasian	527/263	70.6±11.9	45.5	NA
Domingues-Montanari 2	2010	Portugal	Caucasian	565/518	52.4±9.3	36.1	NA
Bondarenko	2011	Russia	Caucasian	1320/467	67 ± 12.6	NA	NA
Baraal	2013	USA	Caucasian	202/487	83.4 ± 5.7	59	NA
Diakite	2016	Morocco	Caucasian	175/201	57.1 ± 2	NA	Cardioembolic

ALOX5AP rs10507391 polymorphism and ischemic stroke risk in allele model was measured by ORs and 95% CIs. The random-effects model was used. The statistical significance of summary OR was determined with Z test. Between-study heterogeneity was assessed by Chi-square test, and was quantified using the *I*<sup>2</sup> statistic (ranging from 0 to 100%), which was defined as the percentage of the observed between-study variability that is due to heterogeneity rather than chance. Data analysis was performed using Revman 5.1.

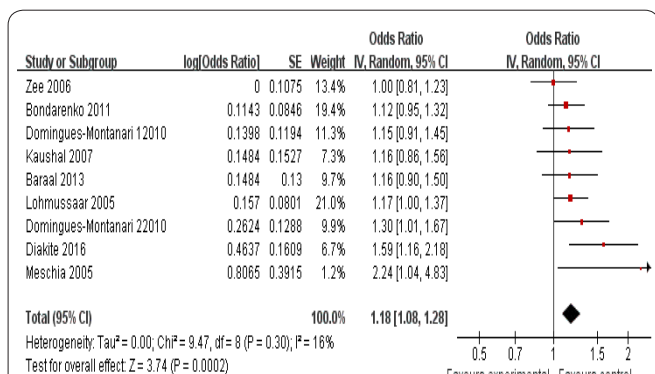
**Results**

**Characteristics of the studies**

The main study characteristics are summarized in Table 1. Nine case-control studies with 4198 patients and 3699 controls were included in this meta-analysis. There was one study with males. All these studies were conducted in Caucasians.

**Meta-analysis**

A significant association was found between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in Caucasians (OR=1.18; 95%CI, 1.08–1.28; *P*=0.0002; Figure 1). ALOX5AP rs10507391 polymorphism was associated with ischemic stroke risk in Caucasians from Europe (OR=1.20; 95%CI, 1.09–1.32; *P*=0.0002; Figure 2) but not from other countries (OR=1.13; 95%CI, 0.95–1.36; *P*=0.17; Figure 2). No significant association was found between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in males (OR=1.12; 95%CI, 0.91–1.39; *P*=0.28; Figure 3). Moreover, ALOX5AP rs10507391 polymorphism was

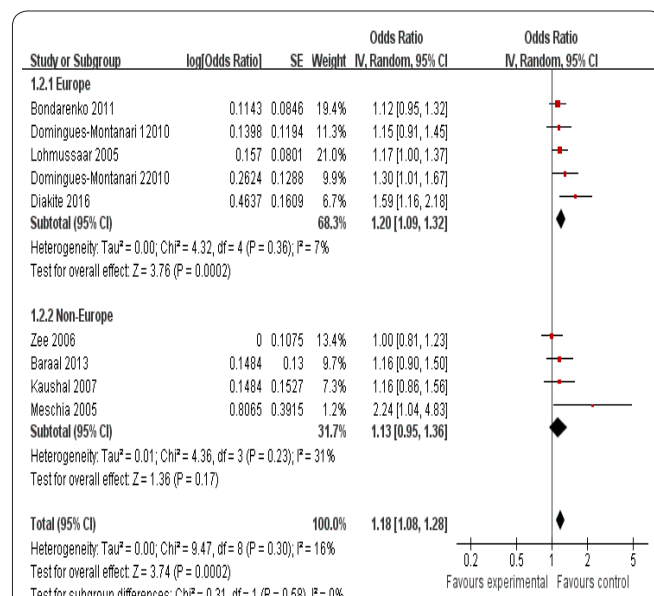


**Figure 1.** The association between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in Caucasians.

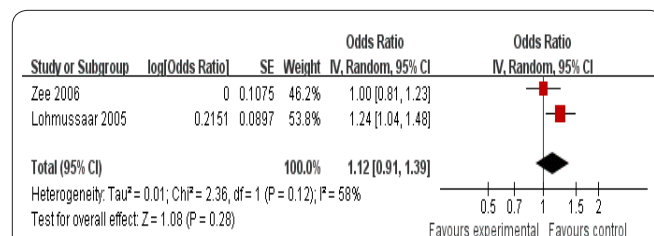
not associated with cardioembolic ischemic stroke risk (OR=1.04; 95%CI, 0.73–1.48; *P*=0.84; Figure 4). The main results are summarized in Table 2.

**Discussion**

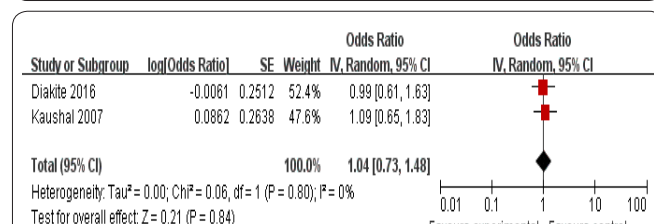
Nine case-control studies with 4198 patients and



**Figure 2.** Subgroup analysis of the association between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in Caucasians.



**Figure 3.** The association between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in males.



**Figure 4.** The association between ALOX5AP rs10507391 polymorphism and cardioembolic ischemic stroke risk.

**Table 2.** Results of the meta-analysis.

	OR (95% CI)	P	P <sub>heterogeneity</sub>
Overall	1.18 (1.08-1.28)	0.0002	0.30
Europe	1.20 (1.09-1.32)	0.0002	0.36
Non-Europe	1.13 (0.95-1.36)	0.17	0.23
Male	1.12 (0.91-1.39)	0.28	0.12
Cardioembolic	1.04 (0.73-1.48)	0.84	0.80

3699 controls were included in this meta-analysis. A significant association was found between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in Caucasians. ALOX5AP rs10507391 polymorphism was associated with ischemic stroke risk in Caucasians from Europe but not from other countries. No significant association was found between ALOX5AP rs10507391 polymorphism and ischemic stroke risk in males. Moreover, ALOX5AP rs10507391 polymorphism was not associated with cardioembolic ischemic stroke risk.

He *et al.* suggested that rs10507391, rs4769874 and its haplotypes in ALOX5AP are unrelated to ACS risk in the Chinese Han population (15). Ke *et al.* indicated that ALOX5AP rs10507391/SG13S114 A>T polymorphism is not associated with the risk of cerebral infarction in the Chinese population (16). Zhang *et al.* indicated that ALOX5AP (rs12876893) was found to be significantly associated with SLE (17). Holloway *et al.* suggested that carriers of both ALOX5AP SG13S41 and LTA4H rs1978331 alleles had an increased risk of developing asthma (18).

Some limitations should also be addressed. First, the number of included studies was small. Second, lacking of the original data of included studies limited the evaluation of the effects of the gene-environment and gene-gene interactions in fracture development. Third, we cannot exclude the possibility of undetected bias. Fourth, we could not do *in vitro* experiments. Finally, the results should be adjusted by other covariates. However, we could not abstracted from studies.

In conclusion, this study found that ALOX5AP rs10507391 polymorphism was associated with ischemic stroke risk in Caucasians.

### Disclosure of conflict of interest

The authors have declared that no competing interests exist.

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