



Association between the polymorphism (rs17222919, -1316T/G) of 5-lipoxygenaseactivating protein gene (ALOX5AP) and the risk of stroke

A meta analysis

Hui Ye, MD, Xin Zhang, MD, Zupeng Chen, MD, PhD, Xu Li, MD, Tiehui Zhang, MD, PhD, Chao Yang, MD, Lifa Huang, MD^{*}

Abstract

Background: The objective of this study was to evalutate the relationship between 5-lipoxygenase-activating protein gene (ALOX5AP) -rs17222919-1316T/G polymorphisms and the risk of stroke.

Methods: Relative studies were searched in January 2018. Case–control studies with extractable data were selected. Four gene models were analyzed including, allele genetic model (G vs T), additive genetic model (GG vs TT, GT vs TT), recessive genetic model (GG vs GT + TT), and dominant genetic model (GG + GT vs TT). Effect sizes included odds ratio (OR) and 95% confidence interval (CI). Heterogeneity was assessed by using Q test and l^2 test. Publication bias was evaluated by using Egger method. The reliability of the results was assessed with sensitivity analysis. All the data analysis was performed with R 3.10 software.

Results: A total of 5 studies inclusing 8492 patients were included. There were significant relationship between ALOX5AP-rs17222919-1316T/G polymorphisms and stroke under all models (P < .05) except the additive genetic model GT versus TT (P > .05). No publication bias was noted. Sensitivity analysis indicated that the results were not stable.

Conclusion: This meta-analysis indicates that ALOX5AP-rs17222919-1316T/G may be a protective factor aginst stroke.

Abbreviations: ALOX5AP = 5-lipoxygenase-activating protein gene, IS = ischemic stroke.

Keywords: ALOX5AP protein, human, meta-analysis, polymorphism, single nucleotide, stroke

Key Points

- This is meta-analysis of *ALOX5AP* polymorphism -rs17222919-1316T/G and stroke.
- A total of 5 studies inclusing 8492 patients were included.
- Signifiant relationship between ALOX5AP-rs17222919-1316T/G polymorphism was found.
- No publication bias was noted.
- Sensitivity analysis indicated that the results were not stable.

Editor: Fabricio Oliveira.

Funding/support: This work was supported by grants from the Zhejiang Provincial Natural Science Foundation of China (No. LY16C090004).

The authors have no conflicts of interest to disclose.

Department of Neurosurgery, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China.

* Correspondence: Lifa Huang, Department of Neurosurgery, the First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, China (e-mail: jazzle@163.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2018) 97:41(e12682)

Received: 16 March 2018 / Accepted: 7 September 2018 http://dx.doi.org/10.1097/MD.000000000012682

1. Introduction

Stroke is an acute cerebrovascular disease that occurs when the blood supply to brain neurons is disrupted by either blockage (ischemic stroke, IS) or a bleeding (hemorrhagic stroke).^[1] It is the second most common life-threaten disease worldwide.^[2] The incidence of IS is higher than hemorrhagic stroke, accounting for 80% of the total stroke.^[2] In recent years, the relationship of stroke susceptibility and genetic tendency gradually attracted people's attention.

The pathophysiology of stroke is complex and involves excitotoxicity mechanisms, inflammatory pathways, oxidative damage, ionic imbalances, apoptosis, angiogenesis, and neuroprotection.^[3] In genetic test, arachidonate 5-lipoxygenase-activating protein gene (ALOX5AP) is found to be involved in the stroke. It encodes 5-lipoxygenase, an arachidonic acid metabolites which is critical for inflammatory responses.^[4,5] Currently, a large amount of literatures have reported the relationship between stroke and ALOX5AP by clinical trials^[6–14] and meta-analysis,^[15,16] focusing on SG13S25G (rs17222814, promoter, G/A), SG13S114T (rs1050739), and other sites. However, the results about the site of rs17222919 were controversial, and no study evaluated the site of rs17222919 by meta-analysis. Therefore, we conducted this meta-analysis to explore the relationship between rs17222919 and stroke by combining the published results.

2. Materials and methods

2.1. Data sources

Search strategies were as follows: English electronic literatures were searched in PubMed (http://www.ncbi.nlm.nih.gov/



Table 1

The basic characteristics of the selected studies.

		Location			IS subjects				Control subjects				
Author	Public year		Study year	NOS score	N	Male/female	Age, y (mean \pm SD)	N	Male/female	Age, y (mean \pm SD)			
Fan	2015	China	NA	7	910	479/431	56.1 ± 10.6	925	478/447	55.3 ± 10.3			
Fan	2015	China	NA	7	1003	542/461	60.5 ± 7.8	889	458/431	59.6 ± 7.4			
Kim	2011	Korea	2007.10-2009.12	7	117	64/53	65.5±12.1	398	194/204	53.8±15.2			
Wang	2012	China	2008-2011	8	658	392/266	69.42 ± 10.58	704	388/316	69.22±9.04			
Yang	2016	China	NA	6	810	416/394	57.7±8.6	825	428/397	55.3 ± 7.2			
Wang	2013	China	2010.9-2011.12	7	622	314/308	56.8 ± 10.2	631	321/310	55.9 ± 10.7			

IS=ischemic stroke, NA=not available, NOS=Newcastle-Ottawa scale, SD=standard deviation.

Table 2

The distribution of genotypes.

		IS subjects				Control subjects				HWE in control		
Author	Public year	ΤΤ	TG	GG	Т	G	TT	TG	GG	Т	G	Р
Fan	2015	593	288	29	1474	346	550	327	48	1427	423	.947
Fan	2015	658	312	33	1628	378	529	313	47	1371	407	.937
Kim	2011	234	145	19	613	183	71	40	6	182	52	.906
Wang	2012	417	219	22	1053	263	469	207	26	1145	259	.600
Yang	2016	525	258	27	1308	312	486	296	43	1268	382	.811
Wang	2013	415	189	18	1019	225	379	221	31	979	283	.867

It was evaluated using the likelihood-ratio chi-square test, P-values were presented. P<.05 was considered representative of a departure from HWE.

 ${\sf HWE}\,{=}\,{\sf Hardy}{-}{\sf Weinberg}\ {\sf equilibrium},\ {\sf IS}\,{=}\,{\sf ischemic}\ {\sf stroke}.$

	Evenerimen	- tal	C 1					Weisch4	Mainht	
Study	Experiment Events To	otal	Events	Total	Odds Ratio	OR	95%-CI	(fixed)	(random)	
ollay						•		(11104)	()	
Fan YJ1 2015	346 1	820	423	1850	<u> </u>	0.79	[0.68; 0.93]	22.8%	19.7%	
Fan YJ2 2015	378 2	006	407	1778		0.78	[0.67; 0.92]	23.5%	19.9%	
Kim DH 2011	52	234	183	796		0.96	[0.67; 1.36]	4.3%	8.1%	
Wang Y 2012	263 1	316	259	1404		1.10	[0.91; 1.34]	13.5%	16.9%	
Yang DZ 2016	312 1	620	382	1650		0.79	[0.67; 0.94]	20.5%	18.9%	
Wang YF 2013	225 1	244	283	1262		0.76	[0.63; 0.93]	15.4%	16.5%	
Fixed effect model	8	240		8740		0.83	10 77 0 901	100.0%		
Random effects model	1	210		0140		0.84	[0.75: 0.95]		100.0%	
Heterogeneity: $I^2 = 55\%$, a	$t^2 = 0.0111, \mu$	p = 0.	.05		r					
A	1.2				0.75 1 1.5					
	Experimer	ntal	Cc	ontrol				Weight	Weight	
Study	Events To	otal	Events	Total	Odds Ratio	OR	95%-CI	(fixed)	(random)	
									•	
FGn YJ1 2015	288	881	327	877		0.82	[0.67; 0.99]	22.7%	20.1%	
FGn YJ2 2015	312	970	313	842		0.80	[0.66; 0.97]	23.4%	20.3%	
Kim DH 2011	40	111	145	379 -	<u> </u>	0.91	[0.59; 1.41]	4.3%	7.1%	
WGng Y 2012	219	636	207	676		1.19	[0.94; 1.50]	13.5%	17.1%	
YGng DZ 2016	258	783	296	782		0.81	[0.66; 0.99]	20.4%	19.0%	
WGng YF 2013	189	604	221	600		0.78	[0.62; 0.99]	15.7%	16.5%	
Fixed offect model	2	005		44EC	e e	0.06	10 79. 0 041	100 0%		
Random effects model	ى ا	905		4150		0.00	[0.76, 0.94]	100.0%	100.0%	
Heterogeneity: $l^2 = 47\%$	$r^2 = 0.0120$	n = 0	09			0.07	[0.70, 0.33]	1000	100.078	
B	- 0.0120, p	0 - 0.	00		0.75 1 1.5					
B	Europine		C -					Mainh4	Mainht	
Study	Experiment	otal	Evente	Total	Odda Patio	OP	05%-01	(fixed)	(random)	
Study	Events it	otai	Evenus	Total		UK	95%-CI	(lixeu)	(ranuoni)	
FGn YJ1 2015	29	622	48	598		0.56	[0.35: 0.90]	23.4%	22.1%	
FGn YJ2 2015	33	691	47	576	· · · · · · · · · · · · · · · · · · ·	0.56	[0.36; 0.89]	24.5%	23.6%	
Kim DH 2011	6	77	19	253		1.04	[0.40; 2.71]	4.1%	5.5%	
WGng Y 2012	22	439	26	495		0.95	[0.53; 1.70]	11.7%	14.7%	
YGng DZ 2016	27	552	43	529		0.58	[0.35; 0.96]	21.0%	20.2%	
WGng YF 2013	18	433	31	410 ·		0.53	[0.29; 0.96]	15.3%	14.0%	
		~ · · ·								
Fixed effect model	2	814		2861		0.63	[0.50; 0.78]	100.0%	100 0%	
Heterogeneity: $I^2 = 0\% \tau^2$	$= 0 \ n = 0.5$	7				0.03	[0.50; 0.76]		100.0%	
C	- 0, p - 0.0	'			0.5 1 2					
U										
	Exporimo	ntal	64	ntrol				Moight	Woight	
Study	Experiment Events To	otal	Evente	Total	Odds Ratio	OR	95%-CI	(fixed)	(random)	
olddy	Events it	Juli	Lvento	Iotai	Odda Natio	OIL	5570 01	(inceu)	(random)	
FGn YJ1 2015	20									
FGn YJ2 2015	29	910	48	925		0.60	[0.38; 0.96]	23.3%	22.1%	
	33 1	910 003	48 47	925 889		0.60 0.61	[0.38; 0.96] [0.39; 0.96]	23.3% 24.4%	22.1% 23.6%	
Kim DH 2011	29 33 10 6	910 003 117	48 47 19	925 889 398		0.60 0.61 1.08	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77]	23.3% 24.4% 4.1%	22.1% 23.6% 5.5%	
Kim DH 2011 WGng Y 2012	29 33 1 6 22	910 003 117 658	48 47 19 26	925 889 398 702		0.60 0.61 1.08 0.90	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60]	23.3% 24.4% 4.1% 12.3%	22.1% 23.6% 5.5% 14.6%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016	29 33 1 6 22 27	910 003 117 658 810	48 47 19 26 43	925 889 398 702 825		0.60 0.61 1.08 0.90 0.63	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03]	23.3% 24.4% 4.1% 12.3% 20.8%	22.1% 23.6% 5.5% 14.6% 20.2%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013	29 33 1 6 22 27 18	910 003 117 658 810 622	48 47 19 26 43 31	925 889 398 702 825 631		0.60 0.61 1.08 0.90 0.63 0.58	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013	29 33 11 6 22 27 18	910 003 117 658 810 622	48 47 19 26 43 31	925 889 398 702 825 631		0.60 0.61 1.08 0.90 0.63 0.58	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model	29 33 11 6 22 27 18 4	910 003 117 658 810 622 120	48 47 19 26 43 31	925 889 398 702 825 631		0.60 0.61 1.08 0.90 0.63 0.58 0.66	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\% r^2$	29 33 11 6 22 0 27 1 18 0 4	910 003 117 658 810 622 120	48 47 19 26 43 31	925 889 398 702 825 631 4370		0.60 0.61 1.08 0.90 0.63 0.58 0.66	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, τ^2	29 1 33 11 6 22 0 27 1 18 0 4 27 1 18 0	910 003 117 658 810 622 120 5	48 47 19 26 43 31	925 889 398 702 825 631 4370		0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D	29 33 11 33 11 6 22 1 27 4 18 4 1 2 1 2 1 2 2 1 2 2 2 2 2 2 2 2 2 2 2 2 2	910 003 117 658 810 622 120 5	48 47 19 26 43 31	925 889 398 702 825 631 4370		0.60 0.61 1.08 0.90 0.63 0.58 0.66	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83]	23.3% 24.4% 12.3% 20.8% 15.1%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D	29 = 3 33 = 10 22 = 0 27 = 4 18 = 0 4^{2} Experiment Experiment	910 003 117 658 810 622 120 5 ntal	48 47 19 26 43 31	925 889 398 702 825 631 4370		0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D Study	29 3 33 10 6 22 0 27 4 18 0 4 1 Experiments To	910 003 117 658 810 622 120 5 ntal otal	48 47 19 26 43 31 31 Co Events	925 889 398 702 825 631 4370	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 OR	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed)	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random)	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D Study FGn YJ1 2015	29 3 33 10 6 22 0 27 4 18 0 4 Experiment Events To 317 4	910 003 117 658 810 622 120 5 ntal otal 910	48 47 19 26 43 31 31 Co Events 375	925 889 398 702 825 631 4370 Total 925	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 OR	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-Cl [0.65; 0.95]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D Study FGn YJ1 2015 FGn YJ2 2015	29 3 33 10 6 22 0 27 3 18 0 4 1 5 = 0, p = 0.79 Experiments Events To 317 9 345 10	910 003 117 658 810 622 120 5 ntal ptal 910 003	48 47 19 26 43 31 31 Co Events 375 360	925 889 398 702 825 631 4370 4370 Total 925 889	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.66	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-Cl [0.65; 0.95] [0.64; 0.93]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011	29 3 33 10 6 22 0 27 3 18 0 27 4 18 0 4 5 0, p = 0.75 Experiment Events To 317 5 345 10 46	910 003 117 658 810 622 120 5 ntal otal 910 003 117	48 47 19 26 43 31 31 Co Events 375 360 164	925 889 398 702 825 631 4370 4370	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.77 0.92	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-CI [0.65; 0.95] [0.64; 0.93] [0.61; 1.41]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8% 7.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%, \tau^2$ D Study FGn YJ1 2015 FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012	29 33 10 33 10 22 0 27 3 18 0 4^{2} = 0, p = 0.75 Experiment Events Tot 317 10 317 10 46 241 0	910 003 117 658 810 622 120 5 ntal 003 117 658	48 47 19 26 43 31 Co Events 375 360 164 233	925 889 398 702 825 631 4370 4370 500000000000000000000000000000000000	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.66 0.77 0.92 1.16	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-CI [0.65; 0.95] [0.64; 0.93] [0.61; 1.41] [0.93; 1.45]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2% 13.4%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8% 7.9% 7.9%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%, \tau^2$ D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012 YGng DZ 2016	29 = 3 33 = 11 6 22 = 0 27 = 3 18 = 0 4 27 = 0, p = 0.73 Experiment Experiment 317 = 12 345 = 11 46 241 = 12 285 = 3	910 003 117 658 810 622 120 5 ntal 003 117 658 810	48 47 19 26 43 31 Co Events 375 360 164 233 339	925 889 398 702 825 631 4370 4370 500000000000000000000000000000000000	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.77 0.72 1.16 0.78	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.32; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-CI [0.65; 0.95] [0.64; 0.93] [0.61; 1.41] [0.93; 1.45] [0.64; 0.95]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2% 13.4% 20.4%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% — 100.0% Weight (random) 19.6% 19.8% 7.9% 17.1% 18.8%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%, \tau^2$ D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013	29 3 33 10 6 22 0 27 4 18 0 27 4 18 0 4 27 4 27 4 18 0 4 27 4 27	910 003 117 658 810 622 120 5 ntal 003 117 658 810 622	48 47 19 26 43 31 Co Events 375 360 164 233 339 252	925 889 398 702 825 631 4370 4370 701 701 701 701 889 398 702 825 631	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.76 0.78 0.77 0.92 1.16 0.78 0.75	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.32; 1.04] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-CI [0.65; 0.95] [0.64; 0.93] [0.64; 0.95] [0.64; 0.95] [0.64; 0.95]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2% 13.4% 20.4% 15.7%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% — 100.0% Weight (random) 19.6% 19.8% 7.9% 7.1% 18.8% 16.6%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013	29 33 10 33 10 6 22 0 27 4 18 0 4 27 4 27 4 18 0 4 27 4 27 4 20 7 20 7 2	910 003 117 658 810 622 120 5 ntal 003 117 658 810 622	48 47 19 26 43 31 Co Events 375 360 164 233 339 252	925 889 398 702 825 631 4370 4370 0 trol 925 889 398 702 8 25 631	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.76 0.78 0.77 0.92 1.16 0.78 0.75	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.32; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-CI [0.65; 0.95] [0.64; 0.93] [0.64; 0.95] [0.64; 0.95] [0.64; 0.95]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2% 13.4% 20.4% 15.7%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8% 7.9% 17.1% 18.8% 16.6%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%, \tau^2$ D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Pandom offer model	29 33 10 33 10 6 22 0 27 4 18 0 4 27 4 18 0 4 27 4 18 0 27 4 18 0 27 4 18 0 27 4 18 0 27 4 285 10 207 0 241	910 003 117 658 810 622 120 5 ntal 003 117 658 810 622 120	48 47 19 26 43 31 Co Events 375 360 164 233 339 252	925 889 398 702 825 631 4370 4370 925 889 398 702 839 8398 702 631 4370	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.77 0.92 1.16 0.78 0.75 0.83	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-CI [0.65; 0.95] [0.64; 0.93] [0.64; 0.93] [0.64; 0.95] [0.64; 0.95] [0.64; 0.94]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2% 13.4% 20.4% 15.7% 100.0%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8% 7.9% 17.1% 18.8% 16.6%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneitie: $l^2 = 55\%$	29 3 10 33 10 22 0 27 4 18 0 4 1 18 0 4 1 20, p = 0.73 Experiment Experiment 345 10 46 241 0 285 4 207 0 46 207 0 47 46 207 0 46 207 0 47	910 003 117 658 810 622 120 5 ntal 003 117 658 810 622 120	48 47 19 26 43 31 Co Events 375 360 164 233 339 252	925 889 398 702 825 631 4370 4370 925 889 398 702 825 631 4370	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.77 0.92 1.16 0.75 0.83 0.84	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-Cl [0.65; 0.95] [0.64; 0.93] [0.64; 0.95] [0.64; 0.95] [0.66; 0.94] [0.76; 0.91] [0.73; 0.96]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2% 13.4% 20.4% 15.7%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8% 7.9% 17.1% 18.8% 16.6%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: / ² = 0%, τ ² D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: / ² = 55%, τ E	29 = 3 33 = 11 6 22 = 0 27 = 3 18 = 0 4 1 = 0, p = 0.72 Experimential Experimential 345 = 11 46 241 = 0 285 = 1 207 = 0 4 1 = 0 285 = 1 207 = 0 4 1 = 0 1 = 0 285 = 1 285 = 1 287 = 1 46 = 1 285 = 1 287 = 1 46 = 1 285 = 1 285 = 1 47 = 1 285 = 1 47 = 1 47 = 1 10 =	910 003 117 658 810 622 120 5 ntal 003 117 658 810 622 120 0 = 0.	48 47 19 26 43 31 Cc Events 375 360 164 233 339 252 05	925 889 398 702 825 631 4370 4370 925 889 398 702 825 631 4370	0.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.66 0.77 0.92 1.16 0.78 0.75 0.83 0.84	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-Cl [0.65; 0.95] [0.64; 0.93] [0.64; 0.95] [0.64; 0.95] [0.66; 0.94] [0.76; 0.91] [0.73; 0.96]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% 22.7% 23.5% 4.2% 13.4% 20.4% 15.7% 100.0%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8% 7.9% 17.1% 18.8% 16.6%	
Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: / ² = 0%, τ ² D Study FGn YJ1 2015 FGn YJ2 2015 Kim DH 2011 WGng Y 2012 YGng DZ 2016 WGng YF 2013 Fixed effect model Random effects model Heterogeneity: / ² = 55%, τ E	29 = 3 33 = 11 6 22 = 0 27 = 1 18 = 0 27 = 1 18 = 0 4 10 = 0 27 = 0 18 = 0 27 = 0 18 = 0 27 = 0 27 = 0 345 = 11 46 = 241 285 = 207 4 10 = 207 4 10 = 0 10 =	910 003 117 658 810 622 120 5 ntal 003 117 658 810 003 117 658 810 003 117 003 117 003 003 117 003 003 003 003 003 003 003 00	48 47 19 26 43 31 Cc Events 375 360 164 233 339 252 05	925 889 398 702 825 631 4370 925 889 398 702 825 631 4370	O.5 1 2 Odds Ratio	0.60 0.61 1.08 0.90 0.63 0.58 0.66 0.66 0.66 0.66 0.77 0.92 1.16 0.78 0.75 0.83 0.84	[0.38; 0.96] [0.39; 0.96] [0.42; 2.77] [0.50; 1.60] [0.38; 1.03] [0.32; 1.04] [0.53; 0.82] [0.53; 0.83] 95%-Cl [0.65; 0.95] [0.64; 0.93] [0.64; 0.93] [0.64; 0.95] [0.64; 0.95] [0.60; 0.94] [0.76; 0.91] [0.73; 0.96]	23.3% 24.4% 4.1% 12.3% 20.8% 15.1% 100.0% Weight (fixed) 22.7% 23.5% 4.2% 13.4% 20.4% 15.7%	22.1% 23.6% 5.5% 14.6% 20.2% 13.9% 100.0% Weight (random) 19.6% 19.8% 7.9% 17.1% 18.8% 16.6%	

pubmed) and Embase (http://www.embase.com); Chinese electronic literatures were searched in Wanfang and China National Knowledge Infrastructure databases. The keywords included stroke or "cerebral apoplexy," ALOX5AP gene, rs17222919

Figure

(rs17222919, -1316T/G). The retrieval deadline was January 2018. This study was a meta-analysis of previous studies on IS patients and did not involve animal experiments; therefore, no ethical review was needed.

Meta-analysis results of all models.

	Total gene		Test of association			Model	Test	of heterogene	Egger test [‡]		
Туре	Cases	Control	OR (95%CI)	Z	Р		Q	Р	ľ, %	Т	Р
G vs T	8240	8740	0.8436 [0.7515; 0.9469]	2.88	0.0039	Random	11.08	0.0498	54.9	0.8834	.4269
GT vs TT	3985	4156	0.8601 [0.7842; 0.9432]	3.20	0.0300	Fixed	9.39	0.0945	46.8	0.4899	.6498
GG vs TT	2814	2861	0.6265 [0.5012; 0.7831]	4.11	< 0.0001	Fixed	3.86	0.5703	0	1.9531	.1225
GG vs GT+TT	4120	4370	0.6614 [0.5302; 0.8249]	3.67	0.0002	Fixed	2.65	0.7534	0	2.3549	.0781
GG+GT vs TT	4120	4370	0.8396 [0.7320; 0.9631]	2.50	0.0125	Random	11.13	0.0488	55.1	0.6418	.5559

CI = confidence interval, OR = odds ratio.

* Random-effects model was used when the P for heterogeneity test < .05, otherwise the fixed-effect model was used.

 ^{+}P <.05 is considered statistically significant for Q statistics.

* Egger test to evaluate publication bias, P<.05 is considered statistically significant.

Study	Odds Ratio	OR 95%-CI
Omitting Fan YJ1 2015 Omitting Fan YJ2 2015 Omitting Kim DH 2011 Omitting Wang Y 2012 Omitting Yang DZ 2016 Omitting Wang YF 2013		0.86 [0.74; 0.99] 0.86 [0.75; 0.99] 0.83 [0.74; 0.95] 0.79 [0.73; 0.86] 0.86 [0.74; 0.99] 0.86 [0.75; 0.99]
Random effects model		0.84 [0.75; 0.95]
	0.8 1 1.2	5
Study	Odds Ratio	OR 95%-CI
Omitting FGn YJ1 2015 Omitting FGn YJ2 2015 Omitting Kim DH 2011 Omitting WGng Y 2012 Omitting YGng DZ 2016 Omitting WGng YF 2013		0.87 [0.79; 0.97] 0.88 [0.79; 0.98] 0.86 [0.78; 0.94] 0.81 [0.73; 0.89] 0.87 [0.79; 0.97] 0.87 [0.79; 0.97]
Fixed effect model	\sim	0.86 [0.78; 0.94]
В	0.8 1 1.3	25
Study	Odds Ratio	OR 95%-CI
Omitting FGn YJ1 2015 Omitting FGn YJ2 2015 Omitting Kim DH 2011 Omitting WGng Y 2012 Omitting YGng DZ 2016 Omitting WGng YF 2013		0.65 [0.50; 0.83] 0.65 [0.50; 0.83] 0.61 [0.48; 0.77] 0.58 [0.46; 0.74] 0.64 [0.50; 0.82] 0.64 [0.51; 0.82]
Fixed effect model		0.63 [0.50; 0.78]
С	0.5 1	2
Study	Odds Ratio	OR 95%-CI
Omitting FGn YJ1 2015 Omitting FGn YJ2 2015 Omitting Kim DH 2011 Omitting WGng Y 2012 Omitting YGng DZ 2016 Omitting WGng YF 2013		0.68 [0.53; 0.87] 0.68 [0.53; 0.87] 0.64 [0.51; 0.81] 0.63 [0.49; 0.80] 0.67 [0.52; 0.86] 0.68 [0.53; 0.86]
Fixed effect model		0.66 [0.53; 0.82]
D	0.5 1	2
Study	Odds Ratio	OR 95%-CI
Omitting FGn YJ1 2015 Omitting FGn YJ2 2015 Omitting Kim DH 2011 Omitting WGng Y 2012 Omitting YGng DZ 2016 Omitting WGng YF 2013		0.86 [0.72; 1.02] 0.86 [0.73; 1.02] 0.83 [0.72; 0.97] 0.78 [0.71; 0.86] 0.86 [0.72; 1.01] 0.86 [0.73; 1.01]
Random effects model		0.84 [0.73; 0.96]
E	0.8 1 1.2	5

Figure 3. Sensitivity analysis results. (A) G versus T; (B) GT versus TT; (C) GG versus TT; (D) GG versus GT+TT; (E) GG+GT versus TT.

2.2. Document selection criteria

Literature were selected based on the following criteria: a casecontrol study with stroke patients as case group and healthy subjects as control group; study about the relationship between ALOX5AP gene polymorphism on -rs17222919 site and stroke; written in English; and with reports of the number of cases and controls, genotypes, and alleles. Review, report, comments, and letters were excluded.

2.3. Literature data extraction and quality assessment

Two authors (HY and ZC) independently extracted the following data: the first author, year of publication, study countries, research time, number of genotypes in case and control groups, as well as demographic data characteristics (e.g., gender and age composition, etc.). If there was different data extraction, consistent results were obtained through panel discussions with a third author (XL). Quality assessment was performed by using the United States Agency for Healthcare Research and Quality recommended the Newcastle-Ottawa scale^[17]; the evaluation includes 3 aspects with a total of 9 points, wherein the subject selection 4 points, comparability 2 points, and exposure assessment 3 points.

2.4. Statistical analysis

This meta-analysis observed the LOX5AP gene polymorphism on -rs17222919 loci and stroke based on the mutant allele (G) and wild type (T). Four gene models were analyzed including, allele genetic model (G vs T), additive genetic model (GG vs TT, GT vs TT), recessive genetic model (GG vs GT+TT), and dominant genetic model (GG+GT vs TT).

First, Hardy–Weinberg equilibrium test (HWE tests) was conducted on subjects in the control group.^[18] In order to ensure that our research quality study that the control group did not comply with HWE (P < .05) would be rejected.^[19]

Meta-analysis was performed by using the meta-package of R 3.10 software. Effect sizes included odds ratio (OR) and 95% confidence interval (CI). Q test based on $\chi^{2[20]}$ and I^2 statistics were used for heterogeneity assessment. If heterogeneity was statistically significant (P < .05, $I^2 > 50\%$), the merged effect sizes were calculated under the random effects model, otherwise, under the fixed effect model.^[21] Egger method was applied for publication bias detection. Finally, exclusion method was used for sensitivity analysis test by ignoring a study each time to observe the effect of this study on the overall OR.



Figure 4. Funnel plots of all models. (A) G versus 1; (B) G1 versus 11; (C) GG versus TT; (D) GG versus GT+TT; (E) GG+GT versus TT.

3. Results

3.1. General characteristics of the selected literature

Literature search results and literature selection process are shown in Fig. 1. Firstly, 358 documents were searched and 144 repeated documents were excluded. By screening of the title and summary, 177 documents those obviously not meet the inclusion criteria were removed. Then in the remaining 27 documents, 22 were excluded, including 7 reviews, 6 cases reports, 4 studies with repeated crowd, and 5 studies with unacquirable data. Finally, 5 documents^[22–26] were included in this meta-analysis.

The general characteristics of the selected are shown in Table 1. A total of 8492 cases were included, with 4120 cases in the case group and 4372 cases in the control group. The selected documents were published between 2011 and 2016. Basic demographic characteristics: average age 55 to 69 years old without statistical difference between the 2 groups; more male than female (case group 2207/1913, control group 2267/2105); subjects came from China and Korean. Quality assessment showed that all selected documents had high quality (Newcastle-Ottawa scale ranged of 6–8 points). Table 2 shows that all the controls in the selected studies accorded to HWE.

3.2. Quantitative data consolidation

The heterogeneity test showed that for the models G versus T and GG+GT versus TT, the heterogeneity was statistically significant (P < .05, $I^2 > 50\%$), so the random effects were used, while, for GT versus TT, GG versus TT, and GG versus GT+TT, the fixed effect model was chosen due to the homogeneity (P > .05, $I^2 < 50\%$).

Meta-analysis showed except under the additive genetic model GT versus TT (OR = 0.8601, 95% CI: 0.7842–0.9432, P > .05), there were significant relationships between ALOX5AP -rs17222919 polymorphism and stroke under all models (Fig. 2): allelic genetic model (G vs T, OR = 0.8436, 95% CI: 0.7515–0.9469, P < .05), additive genetic model (GG vs TT, OR = 0.6265, 95% CI: 0.5012–0.7831, P < .0001), recessive genetic model (GG vs GT+TT, OR = 0.6614, 95% CI: 0.5302–0.8249, P < .05), and dominant genetic model (GG+GT vs TT, OR = 0.8396, 95% CI: 0.7320–0.9631, P < .05). The results were summarized in Table 3.

3.3. Sensitivity analysis

The sensitivity analysis showed that for the dominant genetic model (GG+GT vs TT), the OR values undergone different changes, while for allele genetic model (G vs T), additive genetic model (GT vs TT), additive genetic model (GG vs TT), and recessive genetic model (GG vs GT+TT), the OR values did not reversed (Fig. 3). The studies Kim $2011^{[23]}$ and Wang $2012^{[24]}$ had significant influence in the overall ORs.

3.4. Assessment of publication bias

Egger method showed no publication bias exists, indicating that the results were reliable (Table 3, Fig. 4).

4. Discussion

Our study was a meta-analysis of previous studies on IS patients. To our knowledge, this is the first meta-analysis on the relationship between ALOX5AP-rs17222919 and stroke. Basing on large sample size (8492 cases), this study makes a reliable conclusion that LOX5AP -rs17222919 gene is a protective gene for stroke.

There are previous meta-analyses on the relationship. Zintzaras et al^[15] found the no evidence of relationship between ALOX5AP gene and stroke by a meta-analysis focusing on HapA haplotype, HapB haplotype, and SG polymorphisms. However, Sophie et al found that in the Iberian population, the SG13S114 (HapB haplotype) variant is an independent risk factor for IS.^[16] Based on the ALOX5AP-rs17222919, the present meta-analysis with all subjects in Asian indicated a strong relationship between ALOX5AP gene and stroke.

The heterogeneity of some models was significant. From the forest plot, the study of Kim $2011^{[23]}$ and Wang $2012^{[24]}$ contribute the high heterogeneity. Except Kim 2011, the subjects of all other studies were IS. The difference in mechanisms of hemorrhagic stroke and IS can lead to different genetic characteristic. The sensitivity analysis also hints the influence of these 2 studies. The heterogeneity can come from other aspects like racial differences in country areas. The subjects of Kim $2011^{[23]}$ came from Korean while those of other studies from Chinese. Other confounding factors, age, sex, living habits, and cultural exchange may also affect the results. However, due to the limited data in the original study, subgroup analysis could not be conducted.

As reported in the original study, ALOX5AP mRNA levels were not compared between cases and controls,^[22,25] which might also be a limitation of this study. Other limitations are listed as follows. Firstly, the potential confounding factors those may affect the meta-analysis were not corrected due to the incomplete data. Secondly, this study only focused on gene polymorphism of 1 gene site rs17222919, which may lead to misjudgment on the overall relationship. Thirdly, sensitive analysis hints that part of the results is not stable. The studies of Kim^[23] and Wang^[24] had significant influence in the overall ORs.

In short, the present meta-analysis showed that rs17222919 genetic polymorphism is a protective factor for stroke. Of course, the conclusion of this study still needs verification by more largescale association analysis or larger sample size study updated meta-analysis.

Author contributions

Lifa Huang and Hui Ye conceived and designed the research. Tiehui Zhang and Chao Yang acquired the data. Xin Zhang, Zupeng Chen, and Xu Li performed the statistical analysis. Lifa Huang drafted the manuscript. All the authors have revised and approved the final version.

Data curation: Tiehui Zhang.

Formal analysis: Chao Yang.

Investigation: Xin Zhang.

Methodology: Zupeng Chen.

Software: Xu Li.

Writing - original draft: Hui Ye.

Writing - review & editing: Lifa Huang.

References

 Alexandrov AW. What is a stroke? in. Acute Stroke Nursing 2010; Wiley-Blackwell, 331, 33–65.

- [2] Donnan GA, Fisher M, Macleod M, et al. Stroke. Lancet 2008;371:1612–23.
- [3] Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: an overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiology 2010;17:197–218.
- [4] Evans J, Ferguson A, Mosley RT, et al. What's all the FLAP about?: 5lipoxygenase-activating protein inhibitors for inflammatory diseases. Trends Pharmacol Sci 2008;29:72–8.
- [5] Helgadottir A, Manolescu A, Thorleifsson G, et al. The gene encoding 5lipoxygenase activating protein confers risk of myocardial infarction and stroke. Nat Genet 2004;36:233–9.
- [6] Löhmussaar E, Gschwendtner A, Mueller JC, et al. ALOX5AP gene and the PDE4D gene in a central European population of stroke patients. Stroke 2005;36:731–6.
- [7] Li ZW, Min YX, Jia S, et al. Polymorphism of SG13S114T/A in the ALOX5AP gene and the risk for stroke in a large Chinese cohort. Acta Genet Sin 2006;33:678–84.
- [8] Meschia JF, Brott TG, Brown RDJr, et al. Phosphodiesterase 4D and 5lipoxygenase activating protein in ischemic stroke. Ann Neurol 2005;58:351–61.
- [9] Kaushal R, Pal P, Alwell K, et al. Association of ALOX5AP with ischemic stroke: a population-based case-control study. Hum Genet 2007;121:601–7.
- [10] Liu J, Kai S, Bai Y, et al. Association of three-gene interaction among MTHFR, ALOX5AP and NOTCH3 with thrombotic stroke: a multicenter case-control study. Hum Genet 2009;125:649–56.
- [11] Helgadottir A, Gretarsdottir S, Clair DS, et al. Association between the gene encoding 5-lipoxygenase-activating protein and stroke replicated in a Scottish population. Am J Hum Genet 2005;76:505–9.
- [12] Zee RY, Cheng S, Hegener HH, et al. Genetic variants of arachidonate 5lipoxygenase-activating protein, and risk of incident myocardial infarction and ischemic stroke: a nested case-control approach. Stroke 2006;37:2007–11.
- [13] Sun H, Wu H, Zhang J, et al. A tagging SNP in ALOX5AP and risk of stroke: a haplotype-based analysis among eastern Chinese Han population. Mol Biol Rep 2011;38:4731–8.
- [14] Wang G, Yao W, Hao S, et al. Variants of the arachidonate 5lipoxygenase-activating protein (ALOX5AP) gene and risk of ischemic stroke in Han Chinese of eastern China. J Biomed Res 2011;25:319–27.
- [15] Zintzaras E, Rodopoulou PN. Variants of the arachidonate 5lipoxygenase-activating protein (ALOX5AP) gene and risk of stroke: a HuGE gene-disease association review and meta-analysis. Am J Epidemiol 2009;169:523–32.
- [16] Domingues-Montanari S, Fernández-Cadenas I, del Rio-Espinola A, et al. Association of a genetic variant in the ALOX5AP with higher risk of ischemic stroke: a case-control, meta-analysis and functional study. Cerebrovasc Dis 2010;29:528–37.
- [17] Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
- [18] Schaid DJ, Jacobsen SJ. Blased Tests of Association: comparisons of allele frequencies when departing from Hardy-Weinberg proportions. Am J Epidemiol 1999;149:706–11.
- [19] Zintzaras E, Lau J. Synthesis of genetic association studies for pertinent gene–disease associations requires appropriate methodological and statistical approaches. J Clin Epidemiol 2008;61:634–45.
- [20] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Int Med 1997;127:820–6.
- [21] Feng R-N, Zhao C, Sun C-H, et al. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. PloS One 2011;6:e18480.
- [22] Fan Y, Chen H, Li A, et al. A promoter polymorphism (rs17222919, -1316T/G) of ALOX5AP gene is associated with decreased risk of ischemic stroke in two independent Chinese populations. PLoS One 2015;10:e0122393.
- [23] Kim DH, Ahn WY, Kim DK, et al. A Promoter polymorphism (rs17222919, -1316T/G) of ALOX5AP is associated with intracerebral hemorrhage in Korean population. Prostaglandins Leukot Essent Fatty Acids 2011;85:115–20.
- [24] Wang Y, Wang GN, Sun H, et al. Association of ALOX5AP with ischemic stroke in eastern Chinese. World J Emerg Med 2012;3:108–13.
- [25] Yang D, Huang X, Cui C, et al. Genetic variants in the transcriptional regulatory region of the ALOX5AP gene and susceptibility to ischemic stroke in Chinese populations. Sci Rep 2016;6:29513.
- [26] Yu-fei W, Cong-cong S, Lian-long J, et al. Interaction of 5-npoxygenaseactivating protein gene polymorphisms and environmental risk factors in ischemic stroke. Chin J Neurol 2013;46:531–5.