Int J Clin Exp Med 2017;10(11):15032-15039
www.ijcem.com /ISSN:1940-5901/IJCEM0056736

Review Article

Association of CRP gene rs1130864 polymorphism with ischemic stroke and coronary artery disease: a meta-analysis

Feng Zhou*, Yanhui Zhou*, Lv Zhou, Tie Guo, Dan Yu

*Department of Neurology, Haikou People's Hospital, Affiliated Haikou Hospital at Xiangya Medical College of Central South University, Haikou, Hainan Province, China. *Equal contributors.*

Received May 4, 2017; Accepted September 22, 2017; Epub November 15, 2017; Published November 30, 2017

Abstract: Objective: CRP is a most commonly used inflammatory marker with atherosclerotic lesions and during the ischemic event. The reported results of the association of SNPs of CRP gene with ischemic stroke and coronary artery disease are not always consistent. We aimed to examine the association of rs1130864 polymorphism with risk of ischemic stroke and coronary artery disease. Methods: We searched human case-control studies in PubMed, Embase, Google Scholar, China National Knowledge Infrastructure and Wanfang database date to April 2017, then summarized the data and used Odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate risk of ischemic stroke and coronary artery disease. We also performed subgroup analyses, sensitivity analyses and publication bias. Results: A total of 11 eligible articles were analyzed. We found rs1130864 polymorphism was not associated with risk of ischemic stroke in dominant model (OR=0.974, 95% CI=0.873-1.086), recessive model (OR=0.886, 95% CI=0.726-1.082), homozygous model (OR=0.889, 95% CI=0.723-1.094), heterozygous model (OR=0.992, 95% CI=0.885-1.111), and allelic model (OR=0.968, 95% CI=0.891-1.052). No significant association between rs1130864 polymorphism and coronary artery disease risk was observed in dominant model (OR=1.018, 95% CI=0.941-1.102), recessive model (OR=1.035, 95% CI=0.908-1.180), homozygous model (OR=1.040, 95% CI=0907-1.193), heterozygous model (OR=1.016, 95% CI=0.935-1.104), and allelic model (OR=1.007, 95% CI=0.947-1.070). Subgroup analysis suggested no relationship between rs1130864 polymorphism and ischemic stroke and coronary artery disease risk was found either in Asian or Caucasian population. Conclusions: This meta-analysis indicated that the CRP gene rs1130864 variant examined may not modulate ischemic stroke and coronary artery disease risk. However, further studies with larger sample sizes and gene-gene interactions as well as gene-environment interactions are warranted.

Keywords: Coronary artery disease, CRP gene, ischemic stroke, meta-analysis, polymorphism

Introduction

Both ischemic stroke (IS) and coronary artery disease (CAD) are considered multiple-factorial diseases, and share risk factors including genetic and environmental factors. In clinical practice, conventional risk factors for IS and CAD can be prevented by changing their lifestyle in most cases [1]. In addition, genetic factors play a vital role in IS and CAD susceptibility and many candidate genes have been reported for their potential roles in IS and CAD, such as ZNF208 gene, GLO1 gene, and CX3CL1 gene [2-4]. However, the recognition on the heritability of IS and CAD remains quite limited.

C-reactive protein (CRP), plays a significant role in acute and chronic inflammation [5]. CRP is a biomarker for atherothrombotic disease and may reflect the level of inflammatory activity within atherosclerotic plaques [6]. Plasma CRP levels are under genetic influence [7]. CRP gene variations may act alone or synergistically to increase risk for IS and CAD, due to its involvement in the regulation of CRP levels. However, Meta-analyses demonstrated little evidence to support a role of CRP gene rs2794521, rs1205, and rs1800947 polymorphisms in IS [8, 9] or CAD risk [10].

It is well-known that rs1130864 locates in the 3' untranslated region of the CRP gene and the

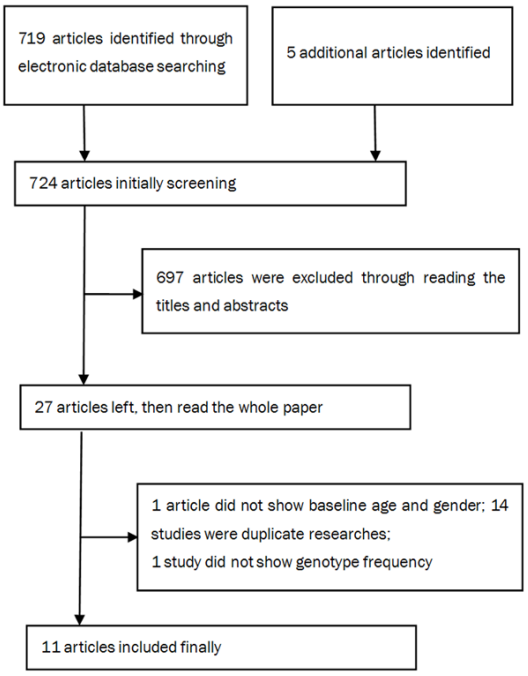

Figure 1. Flow diagram of the literature selection process.

major allele of rs1130864 has been associated with lower circulating CRP levels [11]. CRP gene rs1130864 variation is proposed as a possible genetic biomarker, the T allele of rs1130864 is suggested to be used to predict IS and CAD risk [12, 13, 18], as well as post-stroke functional outcome [14]. However, other studies did not find this polymorphism playing a role in IS and CAD risk [15, 17, 19, 36]. For the above-mentioned inconsistent reports, we performed a meta-analysis to determine whether the risks of IS and CAD were associated with rs1130864 polymorphism.

Methods

Literature retrieval strategy

This meta-analysis was according to the recommendations of the PRISMA statement, and ethical approval was not required. To identify eligible studies on the association of rs1130864 polymorphism and risk of IS and CAD, we performed a literature search of published studies in PubMed, Embase, Google Scholar, China National Knowledge Infrastructure and Wanfang database from 1980 to April 2017. The terms we used are as follows: C-reactive protein or CRP, combined with polymorphism or genetic variants or mutation, as well as ischemic stroke or cerebral infarction or stroke or coronary artery disease or coronary heart disease or ischemic heart disease. Besides, references of all identified studies were inspected for further research.

Selected criteria

Studies were included in the meta-analysis if they met all of the following criteria: (1) used a case-control design with healthy individuals as controls; (2) investigated the association of rs1130864 polymorphism with IS and/or CAD risk; (3) could calculate an odds ratio (OR) and 95% confidence intervals (CI) by crude data; (4) restricted the publication language in English and/or Chinese. The exclusion criteria were as follows: (1) case reports, duplicate studies, comments or animal model studies; (2) studies without detailed genotype frequency distribution; (3) studies focus on IS and CAD recurrence or pharmacogenetics.

Data extraction

Two investigators (Z.F. and G.T.) independently extracted information from each study. All authors discussed to reach a consensus when disagreements arise. Main characteristics including the following data: first author, publication year, subjects' locations, number of cases and controls, genotyping methods, Hardy-Weinberg equilibrium (HWE) in controls, and allele and genotype frequencies. If genotype frequencies were not available in the text of the respective publications, we would contact the authors of primary articles by email. Newcastle-Ottawa Scale (NOS) scores were used to assess the quality of included studies, in which NOS scores > 5 shows a good quality.

Statistical analysis

The HWE of genotype distribution of the controls for all studies was tested using the Chi-square test. Crude ORs with 95% CI were performed to evaluate the relationship between rs1130864 and IS and CAD risk. Pooled ORs were calculated according to the following genetic models: allele (T/C), homozygote (TT/CC), heterozygous (CT/CC), dominant (TT+CT/CC), and recessive model (TT/CT+CC).

The Chi-square-based Q test and the I^2 metric were served to test heterogeneity. If $p > 0.10$ or

Table 1. Characteristics of studies included in the meta-analysis for the association of rs1130864 polymorphism with the risk of IS or CAD

Study	Year	Ethnic group	Nation	Disease	Genotyping Methods	Cases, CC/CT/TT	Controls, CC/CT/TT	NOS score	P_{HWE}
Du et al [15]	2015	Asian	China	IS	PCR-RFLP	142/16/0	248/42/0	6	0.184
Andersson et al [34]	2009	Caucasian	Sweden	IS	TaqMan	139/111/17	284/214/46	7	0.529
Zacho et al [35]	2008	Caucasian	Denmark	IS	TaqMan	356/319/66	4550/4036/949	7	0.218
Huang et al [19]	2016	Asian	China	IS	qPCR	69/27/4	74/30/2	6	0.600
Morita et al [13]	2006	Asian	Japan	IS	TaqMan	132/19/1	265/38/1	7	0.768
Ladenvall et al [29]	2006	Caucasian	Sweden	IS	TaqMan	287/257/56	281/258/61	6	0.875
Brull et al [18]	2003	Caucasian	UK	CAD	PCR-RFLP	86/78/22	122/92/13	7	0.420
Grammar et al [16]	2008	Caucasian	Germany	CAD	PCR-RFLP	1150/1124/281	305/316/76	8	0.664
Pai (1) et al [17]	2008	Caucasian	USA	CAD	TaqMan	125/94/18	238/178/51	7	0.047
Pai (2) et al [17]	2008	Caucasian	USA	CAD	TaqMan	126/98/24	235/205/52	7	0.466
Yan et al [36]	2006	Asian	China	CAD	PCR	114/14/0	107/12/0	7	0.562
Zacho et al [35]	2008	Caucasian	Denmark	CAD	TaqMan	835/767/184	4071/3588/831	7	0.324
Sun et al [37]	2011	Asian	China	CAD	PCR-RFLP	84/13/1	111/13/1	6	0.383

Abbreviations: CAD, coronary artery disease; HWE, Hardy-Weinberg equilibrium; IS, ischemic stroke; NOS, Newcastle-Ottawa scale; PCR-RFLP, polymerase chain reactions restriction fragment length polymorphism.

I^2 < 50%, which means notable homogeneity, and the fixed effects model would be selected to calculate the effects size; otherwise, the random effects model was performed. Sensitivity analysis was carried out to examine the stability and reliability of the combined effects in this meta-analysis. Publication bias of the included studies was evaluated by Begg's test and Egger's test. All statistical data were analyzed using STATA software (version 12.0, STATA Corp., USA). Statistical significance was determined at $p < 0.05$.

Results

Selection and characteristics of studies

Study selection process is graphically represented in **Figure 1**. An initial screening of 224 records matching the search terms were obtained, of which 207 were discarded owing to various reasons and 17 potential articles were identified through carefully reading the titles and abstracts. Of the 17 studies, 1 study did not show baseline age and gender, as well as genotype method; 4 studies were repeated researches; and 1 study did not show genotype frequencies. Therefore, these 6 studies were excluded according to the criteria. Finally, leaving 11 eligible articles met the inclusion criteria and thus were included in the meta-analysis.

The main information of the eligible studies is summarized in **Table 1.** There were 2024 IS cases and 11373 controls from 6 case-control studies to estimate the relationship between rs1130864 polymorphism and IS risk, and 5238 CAD cases and 10617 controls from 7 case-control studies for CAD risk. Deviation from HWE was identified in the genotype distribution of 1 study [17]. Moreover, there was well homogeneity in genotyping measurement, matching age and gender across studies.

Meta-analysis

Table 2 shows the principal results of fixed-effect or random-effect meta-analysis. In general, we did not find any association of rs1130864 polymorphism with IS risk in dominant model (OR=0.974, 95% CI=0.873-1.086), recessive model (OR=0.886, 95% CI=0.726-1.082), homozygous model (OR=0.889, 95% CI=0.723-1.094), heterozygous model (OR=0.992, 95% CI=0.885-1.111), and allelic model (OR=0.968, 95% CI=0.891-1.052). Meta-analysis of CAD risk studies showed a similar trend. No any association of rs1130864 polymorphism with CAD risk was observed in dominant model (OR=1.018, 95% CI=0.941-1.102), recessive model (OR=1.035, 95% CI=0.908-1.180), homozygous model (OR=1.040, 95% CI=0.907-1.193), heterozygous model (OR=1.016, 95% CI=0.935-1.104), and allelic model (OR=1.007, 95% CI=0.947-1.070). Subgroup analysis by ethnicity and HWE deviation suggested a similar non-significant trend toward IS

Table 2. Association of rs1130864 polymorphism with risk of ischemic stroke and coronary artery disease

Genetic model	Overall and subgroups	Ischemic stroke				Coronary artery disease			
		N	OR (95% CI)	P_H	I^2	N	OR (95% CI)	P_H	I^2
T/C	Overall	6	0.968 (0.891-1.052)	0.506	0	7	1.007 (0.947-1.070)	0.777	0
	All in HWE	6	0.968 (0.891-1.052)	0.506	0	6	1.016 (0.954-1.082)	0.840	0
	Caucasian	3	0.982 (0.901-1.071)	0.711	0	4	1.013 (0.951-1.080)	0.656	0
	Asian	3	0.805 (0.588-1.103)	0.315	13.4	2	1.196 (0.696-2.055)	0.751	0
TT/CC	Overall	6	0.889 (0.723-1.094)	0.805	0	7	1.040 (0.907-1.193)	0.158	37.2
	All in HWE	6	0.889(0.723-1.094)	0.805	0	6	1.069 (0.929-1.231)	0.228	29.0
	Caucasian	3	0.873 (0.708-1.077)	0.875	0	4	1.069 (0.928-1.382)	0.132	46.6
	Asian	3	2.109 (0.486-9.156)	0.968	0	2	1.321 (0.081-21.434)	N/A	N/A
CT/CC	Overall	6	0.992 (0.885-1.111)	0.863	0	7	1.016 (0.935-1.104)	0.858	0
	All in HWE	6	0.992 (0.885-1.111)	0.863	0	6	1.017 (0.933-1.108)	0.763	0
	Caucasian	3	1.009 (0.894-1.138)	0915	0	4	1.013 (0.929-1.105)	0.540	0
	Asian	3	0.862 (0.609-1.221)	0.584	0	2	1.202 (0.674-2.142)	0.750	0
TT+CT/CC	Overall	6	0.974 (0.873-1.086)	0.893	0	7	1.018 (0.941-1.102)	0.528	0
	All in HWE	6	0.974 (0.873-1.086)	0.893	0	6	1.027 (0.947-1.114)	0.520	0
	Caucasian	3	0.983 (0.876-1.103)	0.968	0	4	1.024 (0.943-1.112)	0.285	20.8
	Asian	3	0.895 (0.637-1.259)	0.504	0	2	1.205 (0.683-2.129)	0.746	0
TT/CT+CC	Overall	6	0.886 (0.726-1.082)	0.235	0	7	1.035 (0.908-1.180)	0.213	29.7
	All in HWE	6	0.886 (0.726-1.082)	0.235	0	6	1.064 (0.930-1.217)	0.332	12.8
	Caucasian	3	0.871 (0.712-1.066)	0.823	0	4	1.063 (0.929-1.217)	0.209	33.8
	Asian	3	2.125 (0.492-9.171)	0.963	0	2	1.485 (0.092-24.019)	N/A	N/A

Abbreviations: CI, confidence interval; HWE, Hardy-Weinberg equilibrium; N, number of studies; N/A, not applicable; OR, odds ratio; P_H, *P* value for heterogeneity.

and CAD risk. For IS risk meta-analysis, we observed high homogeneity ($P_H > 0.05$, $I^2=0$) in all of the five genetic models. A notable homogeneity ($P_H > 0.05$, $I^2 < 50\%$) existed in each of genetic models and subgroups analysis for CAD risk. **Figure 2** shows the results of IS risk (A) and CAD risk (B) under the dominant model (TT+CT/CC).

Sensitivity analysis

We excluded one single study from the overall pooled analysis and recalculated the pooled ORs to check whether the pooled ORs were materially changed. No individual study significantly affected the recalculated ORs, indicating our results were valuable. **Figure 3** shows the results of sensitivity analysis on the association between rs1130864 polymorphism and IS risk (A) and CAD risk (B) under the dominant model (TT+CT/CC).

Publication bias

Publication bias for IS and CAD risk were evaluated by Begg's test and Egger's test. Funnel plots appeared to be symmetrical and Egger's test did not show statistically significant asymmetry both for IS (dominant model, P_{Egger} =0.532) and CAD (dominant model, P_{Egger} =0.691). **Figure 4** shows symmetrically distributed funnel plot of the association between rs1130864 polymorphism and IS (A) and CAD (B) under the dominant model (TT+CT/CC).

Discussion

Though alterations in plasma CRP levels have biological significance including reflection of inflammation stages and elevated CRP levels are associated with an increased risk of IS and CAD [6, 20-22]. In present meta-analysis, however, we did not find any association in five genetic models between rs1130864 polymorphism and IS risk neither in Asian nor Caucasian population. We also evaluated the association of rs1130864 polymorphism with CAD risk, and the consequences were likely to be the same.

As a well-characterized biomarker of inflammation, CRP is of importance in the initiation, pro-

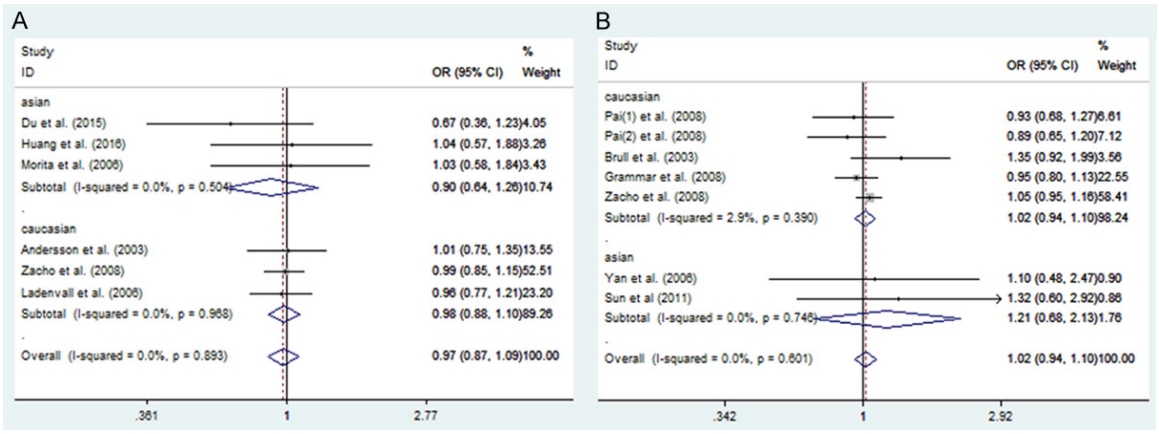

Figure 2. Forest plot of rs1130864 polymorphism and IS risk (A) and CAD risk (B) under the dominant model (TT+CT/CC). Abbreviations: CAD, coronary artery disease; CI, confidence interval; IS, ischemic stroke; OR, odds ratio.

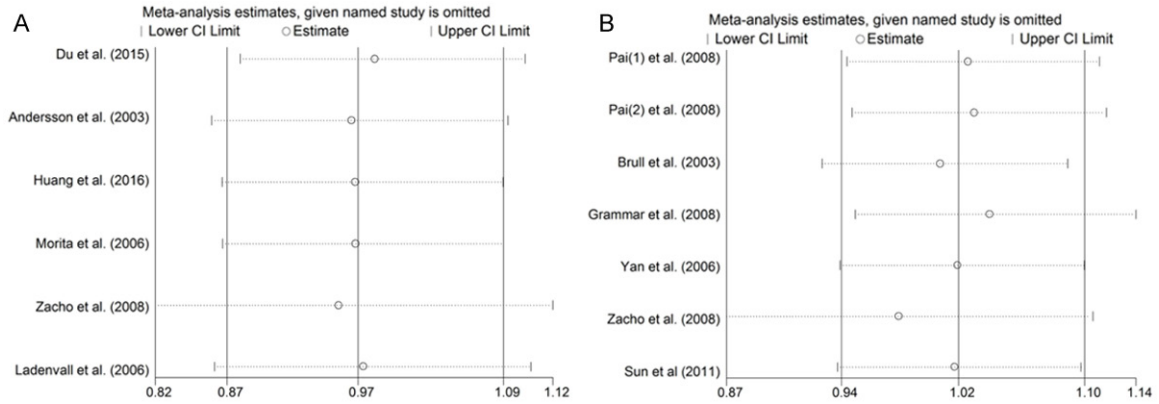

Figure 3. Sensitivity analysis on the association between rs1130864 polymorphism and IS risk (A) and CAD risk (B) under the dominant model (TT+CT/CC). Abbreviations: CAD, coronary artery disease; CI, confidence interval; IS, ischemic stroke.

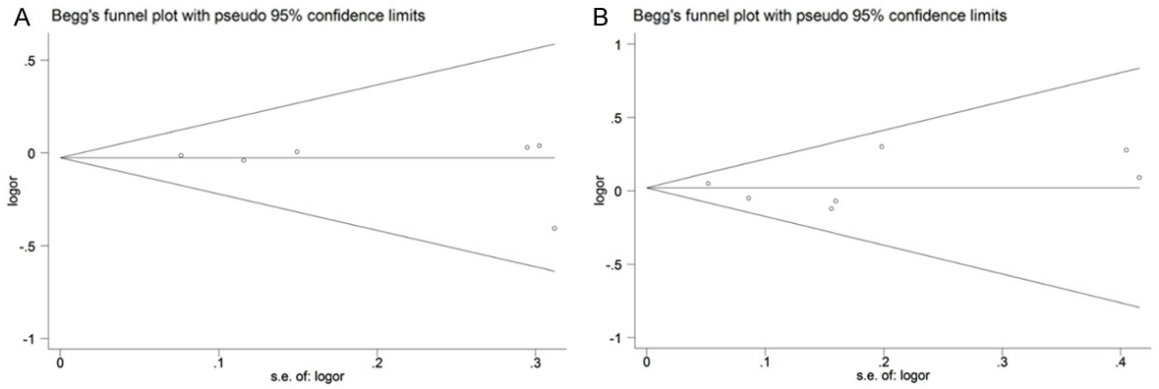

Figure 4. Funnel plot of the association of rs1130864 polymorphism with IS risk (A) and CAD risk (B) under the dominant model (TT+CT/CC). Abbreviations: CAD, coronary artery disease; IS, ischemic stroke; OR, odds ratio.

gression, and clinical outcome of atherosclerosis [5], which through its complications is the leading cause of IS and CAD [21, 34]. In adults, higher CRP levels are positively associated with

larger infarction volumes in acute IS [23], but cannot help in distinguishing TOAST subtypes [24]. Moreover, CRP levels in the very early phase of acute IS is a predictor for the outcome [25]. Among children, the multicenter VIPS (Vascular effects of Infection in Pediatric Stroke) study found that higher levels of CRP were associated with increased recurrent IS [26]. These observations illustrate a clear positive relationship between CRP and ischemic events. In addition, the absolute level of CRP also influenced by age, BMI, smoking, and other clinical or environmental risk factors [7, 27, 28].

Given that SNPs of CRP gene have been showed to be significantly associate with plasma CRP levels in prior association studies [18, 25], which might lead to a significantly increased susceptibility of IS and CAD, a number of researches have been performed to assess the possible relations between CRP gene polymorphisms and IS and CAD risk. Kotlega et al [31] suggested that AA genotype of rs2794521 promotes improvement of neurological state in IS patients. Similarly, Wang et al [32] reported that the A allele frequency for rs2794521 performed a protective effect for against IS. The minor alleles of 2667C associated with lower plasma CRP concentrations in Caucasian were associated with decreased risk of cerebrovascular disease mortality [33]. These findings indicate that some of the CRP gene variations may protect against the malignant progression of IS through decreasing the plasma CRP levels. Nonetheless, several studies suggest completely opposite results. The T allele of 1919A/T is associated with plasma CRP levels and cerebrovascular disease risk in older adults [36]. Kuhlenbaeumer et al [38] suggested that rs1130864 variant was not associated with IS as a whole but strongly associated with microangiopathic stroke. The T allele of rs1130864 showed a significant association with poor functional outcome in IS patients [14], and TT homozygotes variant increases susceptibility to CAD [18].

Although several previous studies indicated that rs1130864 was associated with IS and CAD risk [13, 14, 18, 38], the majority of studies did not show associations among them in all genetic models. Ladenvall et al [29] demonstrated that rs1130864 polymorphism was associated with CRP levels but no association was detected for overall or TOAST subtypes of IS. Shi et al [10] reported that CAD risk was associated with rs2794521 polymorphism but not with rs1130864 polymorphism. In brief, the relationship between rs1130864 polymorphism and IS or CAD risk is not causal [17, 31, 34-37]. In view of these mixed findings, we performed meta-analysis, the pooled results showed that rs1130864 variant examined may not directly modulate IS and CAD risk.

Ethnicity is a well-known factor in determining the genetic variation, as different genetic backgrounds may result in various consequences. Through racial subgroup analysis, the genetic backgrounds among subgroup studies were genetically homogenous. Our results showed a notable homogeneity ($P_H > 0.05$, $I^2 < 50\%$) in all of the five genetic models for IS and CAD risk. Therefore, subgroup results added credibility to the correlation between rs1130864 polymorphism and IS and CAD risk. Subsequently, we performed sensitivity analysis to evaluate the stability of the pooled effect sizes due to baseline of percentage of males and mean age are not exactly the same between-studies. No individual study significantly affected the recalculated ORs, indicating our results were valuable.

This study presents several limitations. Firstly, the pathogenesis of IS and CAD are complex and involves multiple genes, though these studies included some of the same SNPs, estimated haplotypes could not directly pool and summarize. Secondly, most of those studies containing small sample size, which reduced the statistical power. Therefore, comprehension of CRP genetic variation in IS and CAD risk remains unclear. Thirdly, clinical subtype and severity of the diseases were not studied. Lastly, the language of qualified research is limited to English and Chinese, despite the fact that some of our statistical tests do not show evidence of publication bias, some may still exist.

In conclusion, this meta-analysis indicated that rs1130864 polymorphism may not act as modifiers of IS and CAD risk. Genetic variation in such single SNP may not directly relate to the occurrence of IS and CAD since they are considered multiple-factorial diseases. To validate the results, larger scale studies on gene-gene interactions as well as gene-environment interactions are warranted.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Dan Yu, Department of Neurology, Haikou People's Hospital, Affiliated Haikou Hospital at Xiangya Medical College of Central South University, No. 43 People's Road, Haikou 570208, Hainan Province, China. Tel: +86-898-66151148; Fax: +86-898-66151148; E-mail: danjasaon@qq.com

References

[1] Soler EP, Ruiz VC. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. Curr Cardiol Rev 2010; 6: 138-149.

[2] Yu J, Zhou F, Luo D, Wang N, Zhang C, Jin T, Liang X, Yu D. ZNF208 polymorphisms associated with ischemic stroke in a southern Chinese population. J Gene Med 2017; 19.

[3] Mäkinen VP, Civelek M, Meng Q, Zhang B, Zhu J, Levian C, Huan T, Segrè AV, Ghosh S, Vivar J, Nikpay M, Stewart AF, Nelson CP, Willenborg C, Erdmann J, Blakenberg S, O'Donnell CJ, März W, Laaksonen R, Epstein SE, Kathiresan S, Shah SH, Hazen SL, Reilly MP; Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Consortium, Lusis AJ, Samani NJ, Schunkert H, Quertermous T, McPherson R, Yang X, Assimes TL. Integrative genomics reveals novel molecular pathways and gene networks for coronary artery disease. PLoS Genet 2014; 10: e1004502.

[4] Jin SG, Chen GL, Yang SL, Zhao MY. Gene-gene interactions among CX3CL1, LEPR and IL-6 related to coronary artery disease in Chinese Han population. Int J Clin Exp Pathol 2015; 8: 5968-5973.

[5] Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999; 340: 115-126.

[6] Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010; 375: 132-140.

[7] Pankow JS, Folsom AR, Cushman M, Borecki IB, Hopkins PN, Eckfeldt JH, Tracy RP. Familial and genetic determinants of systemic markers of inflammation: the NHLBI Family Heart Study. Atherosclerosis 2001; 154: 681-689.

[8] Liu Y, Geng PL, Yan FQ, Chen T, Wang W, Tang XD, Zheng JC, Wu WP, Wang ZF. C-reactive protein -717A > G and -286C > T > A gene polymorphism and ischemic stroke. Chin Med J (Engl) 2015; 128: 1666-1670.

[9] González-Giraldo Y, Barreto GE, Fava C, Forero DA. Ischemic stroke and six genetic variants in CRP, EPHX2, FGA, and NOTCH3 genes: a meta-analysis. J Stroke Cerebrovasc Dis 2016; 25: 2284-2289.

[10] Shi YJ, Zhang J, Tan C, Xu W, Sun Q, Li JX. Genetic association studies reporting on variants in the C-reactive protein gene and coronary artery disease a meta-analysis. Medicine 2015; 94: e1131.

[11] Suk Danik J, Chasman DI, Cannon CP, Miller DT, Zee RY, Kozlowski P, Kwiatkowski DJ, Ridker PM. Influence of genetic variation in the C-reactive protein gene on the inflammatory response during and after acute coronary ischemia. Ann Hum Genet 2006; 70: 705-716.

[12] Arenillas JF, Massot A, Alvarez-Sabın J, Fernandez-Cadenas I, del Rio-Espinola A, Chacon P, Quintana M,Molina CA, Rovira A, Montaner J. C-reactive protein gene C1444T polymorphism and risk of recurrent ischemic events in patients with symptomatic intracranial atherostenoses. Cerebrovasc Dis 2009; 28: 95-102.

[13] Morita A, Nakayama T, Soma M. Association study between C-reactive protein genes and ischemic stroke in Japanese subjects. Am J Hypertens 2006; 19: 593-600.

[14] Guo J, Yu L, Zhang J, Chen N, Zhou M, He L. CRP gene polymorphism predicts post-stroke functional outcome in Han Chinese. Acta Neurol Scand 2014; 129: 263-268.

[15] Du J, Yu D, Li X, Chen Z, Li J, Gao Y, Zhao J, Yang X. Association study between C-reactive protein polymorphisms and ischaemic stroke. Neurol Res 2015; 3: [Epub ahead of print].

[16] Grammar TB, März W, Renner W, Bohm BO, Hoffmann MM. C-reactive protein genotypes associated with circulating C-reactive protein but not with angiographic coronary artery disease: the LURIC study. Eur Heart J 2009; 30: 170-182.

[17] Pai JK, Mukamal KJ, Rexrode KM, Rimm EB. C-reactive protein gene polymorphisms, CRP levels, and risk of incident coronary heart disease in two nested case-control studies. PLoS One 2008; 3: e1395.

[18] Brull DJ, Serrano N, Zito F, Jones L, Montgomery HE, Rumley A, Sharma P, Lowe GD, World MJ, Humphries SE, Hingorani AD. Human CRP gene polymorphism influences CRP levels: implications for the prediction and pathogenesis of coronary heart disease. Arterioscler Thromb Vasc Biol 2004; 24: 1328.

[19] Huang J, He QC, Yang SB, Jiang W, Xu LL, Wang JP, Jian R, Xu FY. Association between CRP polymorphisms and the risk of ischemic stroke. Int J Clin Exp Pathol 2016; 9: 2241-2246.

[20] Zhou Y, Han W, Gong D, Man C, Fan Y. HS-CRP in stroke: a meta-analysis. Clin Chim Acta 2016; 453: 21-27.

[21] Buerki SE, Grandgirard D, Datta AN, Hackenberg A, Martin F, Schmitt-Mechelke T, Leib SL, Steinlin M, Swiss Neuropediatric Stroke Registry Study Group. Inflammatory markers in pediatric stroke: an attempt to better understanding the pathophysiology. Eur J Paediatr Neurol 2016; 20: 252-260.

[22] Rizzo M, Corrado E, Coppola G, Muratori I, Novo S. Prediction of cerebrovascular and cardiovascular events in patients with subclinical carotid atherosclerosis: the role of C-reactive protein. J Investig Med 2008; 56: 32-40.

[23] Youn CS, Choi SP, Kim SH, Oh SH, Jeong WJ, Kim HJ, Park KN. Serum highly selective C-reactive protein concentration is associated with the volume of ischemic tissue in acute ischemic stroke. Am J Emerg Med 2012; 30: 124-128.

[24] Das S, Roy S, Kaul S, Jyothy A, Munshi A. CRP gene (1059G > C) polymorphism and its plasma levels in ischemic stroke and hemorrhagic stroke in a south Indian population. Inflammation 2014; 37: 1683-1688.

[25] Huang Y, Jing J, Zhao XQ, Wang CX, Wang YL, Liu GF, Wang CJ, Liu LP, Yang XM, Jiao Y, Wang LS, Wang YJ, Gu WK. High sensitivity C-reactive protein is a strong risk factor for death after acute ischemic stroke among Chinese. CNS Neurosci Ther 2012; 18: 261-266.

[26] Fullerton HJ, deVeber GA, Hills NK, Dowling MM, Fox CK, Mackay MT, Kirton A, Yager JY, Bernard TJ, Hod EA, Wintermark M, Elkind MS; VIPS Investigators. Inflammatory biomarkers in childhood arterial ischemic stroke: correlates of stroke cause and recurrence. Stroke 2016; 47: 2221-2228.

[27] Danesh J, Muir J, Wong YK, Ward M, Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins: a population-based study. Eur Heart J 1999; 20: 954-959.

[28] Kathiresan S, Larson MG, Vasan RS, Guo CY, Gona P, Keaney JF Jr, Wilson PW, Newton-Cheh C, Musone SL, Camargo AL, Drake JA, Levy D, O'Donnell CJ, Hirschhorn JN, Benjamin EJ. Contribution of clinical correlates and 13 C-reactive protein gene polymor-phisms to interindividual variability in serum C-reactive protein level. Circulation 2006; 113: 1415-1423.

[29] Ladenvall C, Jood K, Blomstrand C, Nilsson S, Jern C, Ladenvall P. Serum C-reactive protein concentration and genotype in relation to ischemic stroke subtype. Stroke 2006; 37: 2018-2023.

[30] Miller DT, Zee RY, Suk Danik J, Kozlowski P, Chasman DI, Lazarus R, Cook NR, Ridker PM, Kwiatkowski DJ. Association of common CRP gene variants with CRP levels and cardiovascular events. Ann Hum Genet 2005; 69: 623-638.

[31] Kotlega D, Nowacki P, Bialecka M, Kurzawski M, Drozdzik M, Ciecwiez S. Association between CRP gene polymorphism 717A/G, C-reactive protein and neurological deficit in ischemic stroke. J Clin Neurosci 2014; 21: 574-577.

[32] Wang Q, Ding H, Tang JR, Zhang L, Xu YJ, Yan JT, Wang W, Hui RT, Wang CY, Wang DW. C-reactive protein polymorphisms and genetic susceptibility to ischemic stroke and hemorrhagic stroke in the Chinese Han population. Acta Pharmacol Sin 2009; 30: 291-298.

[33] Lange LA, Carlson CS, Hindorff LA, Lange EM, Walston J, Durda JP, Cushman M, Bis JC, Zeng D, Lin D, Kuller LH, Nickerson DA, Psaty BM, Tracy RP, Reiner AP. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. JAMA 2006; 296: 2703-2711.

[34] Andersson J, Johansson L, Ladenvall P, Wiklund PG, Stegmayr B, Jern C, Boman K. C-reactive protein is a determinant of first-ever stroke: prospective nested case-refernt study. Cerebrovas Dis 2009; 27: 544-551.

[35] Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med 2008; 359: 1879-1908.

[36] Yan M, Zhao L, Zheng F, Sun X, Zhang Y, Wang C. The relationship between gene polymorphism and CRP levels in a Chinese Han population. Biocheml Genet 2007; 45: 1-9.

[37] Sun DL, Zhong LJ, Liu Y, Zhang Q, Zhang L, Zhang YM. Relationship of C-reactive protein genetic polymorphisms with chronic periodontitis and coronary heart disease. J Chin Pract Diagn Ther 2011; 25: 219-222.

[38] Kuhlenbaeumer G, Huge A, Berger K, Kessler C, Voelzke H, Funke H, Stoegbauer F, Stoll M, Ringelstein EB. Genetic variants in the C-reactive protein gene are associated with microangiopathic ischemic stroke. Cerebrovasc Dis 2010; 30: 476-82.