MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 3240-3246
DOI: 10.12659/MSM.902327

Received: 2016.11.11
Accepted: 2016.12.26
Published: 2017.07.03

Collagen Type I Alpha 2 (COL1A2) Polymorphism Contributes to Intracranial Aneurysm Susceptibility: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 Qi Gan*
BCDF 2 Qianqian Liu*
DF 1 Xin Hu
ADG 1 Chao You

1 Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan, P.R. China
2 Department of Respiratory Diseases, Chengdu Municipal First People's Hospital, Chengdu, Sichuan, P.R. China

* These authors contributed equally to this manuscript

Corresponding Author: Chao You, e-mail: backinblack77@126.com
Source of support: This work was supported by the National Key Technology R&D Program for the 12th Five-year Plan of P.R. China (No. 2011BAI08B05)

Background: COL1A2, which encodes collagen type I alpha2, has long been suggested to be a potential positional and functional candidate gene for intracranial aneurysm. We performed a meta-analysis to assess the association between COL1A2 rs42524 polymorphism and the risk of intracranial aneurysm.

Material/Methods: We conducted a systematic search for relevant literature from the following databases up to 22 July 2016: PubMed, Embase, Web of Science, and China National Knowledge Infrastructure. The strength of association between gene and disease was estimated using odds ratios (ORs) with 95% confidence intervals (CIs) under 5 genetic models.

Results: A total of 6 qualified studies were enrolled in this meta-analysis. Pooling results indicated a significant association between COL1A2 rs42524 polymorphism and intracranial aneurysm risk under 4 genetic models (C *vs.* G: OR=1.74, 95%CI=1.34–2.26; GC *vs.* GG: OR=1.81, 95%CI=1.37–2.41; CC+GC *vs.* GG: OR=1.74, 95%CI=1.28–2.36; CC *vs.* GC+GG: OR=1.76, 95%CI=1.02–3.04). This association was still robust when stratified by ethnicity, intracranial aneurysm type, or Hardy-Weinberg Equilibrium, which was stronger in Asian than in Caucasians. No publication bias was observed.

Conclusions: This meta-analysis suggests COL1A2 rs42524 is a significant risk factor for IA susceptibility, with an especially strong effect in Asian people. Further larger-scale epidemiological studies among different ethnicities are warranted to confirm our findings.

MeSH Keywords: Collagen Type I • Intracranial Aneurysm • Meta-Analysis • Polymorphism, Genetic

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/902327

2145 2 3 26

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Intracranial aneurysm (IA) is a common cerebrovascular abnormality that is characterized by local ballooning of an intracranial artery. It is estimated that unruptured IA has a prevalence of approximately 2.7–6.5% in the general population and a rupture rate of approximately 1% annually [1–3]. Ruptured IA causes subarachnoid hemorrhage (SAH), which usually leads to catastrophic consequences and has a high mortality rate of approximately 35–50% [4], as well as a high neurological deficit rate [5]. It is therefore of paramount importance to identify asymptomatic patients to remove aneurysms and to avoid secondary hemorrhages.

IA is currently considered to be a multigenic disease. Although it is associated with common modifiable risk factors such as hypertension and smoking [6], genetic factors also play important roles in the etiology of IA. For example, the first-degree relatives of aneurysmal SAH patients have a 4 times higher risk of IA rupture than members of the general population, and the risk increases to 6 times higher among siblings [7,8]. In addition, IAs in a small group of patients are found to occur in the context of heritable connective tissue diseases, including Ehlers-Danlos syndrome type IV, Marfan syndrome, Alport syndrome, and polycystic kidney disease [9,10]. Several candidate genes have been identified as being associated with IA, such as the genes encoding perlecan, versican, tropoelastin, and fibrillin [11]. As these genes may account for only a minority of IAs, the quest to explore the genetic basis of IA is ongoing.

Collagen type I alpha 2 (COL1A2) has long been suggested to be involved in IA pathogenesis. Peters et al. observed significant overexpression of COL1A2 in IA using the superficial temporal artery as a control [12]. In a linkage and association study of IA, Onda et al. found the best evidence of linkage located at D7S2472 on chromosome 7, which is in the vicinity of COL1A2 [13]. Based on these findings, COL1A2 is considered to be a positional and functional candidate gene for IA. Several studies have been conducted to explore the genetic association between COL1A2 and IA. The focus of these studies has been rs42524, which causes an Ala-549 to Pro-549 substitution. Yoneyama et al. found significant differences in the allelic frequency of rs42524 between IA patients and controls in Japan [14], which was validated in a study of the Chinese population [15]. However, several other studies have failed to replicate the association [16]. Considering the small sample size in an individual study, which may lead to insufficient statistical power, we undertook this meta-analysis to evaluate the association between the COL1A2 rs42524 polymorphism and IA risk.

Material and Methods

Publication search

We searched the PubMed, Embase, Web of Science, and China National Knowledge Infrastructure (CNKI) to identify articles addressing the association between COL1A2 rs42524 polymorphism and IA (the last search was conducted on 22 July 2016) using combinations of the following key words: ("polymorphism" OR "genotype" OR "mutation" OR "variant") AND ("aneurysm" OR "subarachnoid hemorrhage") AND ("COL1A2" OR " collagen type I alpha 2" OR "rs42524").

All the references of the retrieved studies were checked by hand search for additional eligible articles. We included all available full text matching the eligible criteria without language restriction.

Inclusion and exclusion criteria

Eligible studies had to meet the following criteria: (a) case-control or cohort study evaluating the association of the COL1A2 rs42524 polymorphism with IA risk; (b) sufficient information were provided for calculating the odds ratios (ORs) and 95% confidence intervals (CIs). The exclusion criteria include secondary publications, reviews, editorials, conference abstracts, and case reports.

Data extraction

Two investigators (Qi Gan and Qianqian Liu) independently reviewed initially identified articles according to pre-specified criteria. Discrepancy was resolved by discussion. The following characteristics of each included study were extracted: the name of first author, publication year, language, country of origin, ethnicity, sample size, genotypes in cases and controls, control source, genotyping method, and type of IA. If key data were not displayed in the original article, we tried to contact the author of the relevant study to obtain missing information.

Statistical analysis

Hardy-Weinberg Equilibrium (HWE) for each study was assessed using Chi-square test in control groups at a significance level of $p<0.05$. I^2 statistic and Cochrane Q test were used to measure heterogeneity. I^2 <50% or $p>0.10$ for the Q test indicated a lack of heterogeneity. The strength of association between COL1A2 rs42524 polymorphism and IA risk was calculated by odds ratio (OR) with 95% confidence interval (CI) using random effects model. The following genetic models were adopted: allelic contrast (C *vs.* G), homozygote contrast (CC *vs.* GG), heterozygote contrast (GC *vs.* GG), dominant model (CC + GC *vs.* GG), and recessive model (CC *vs.* GC +GG). Subgroup analyses

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

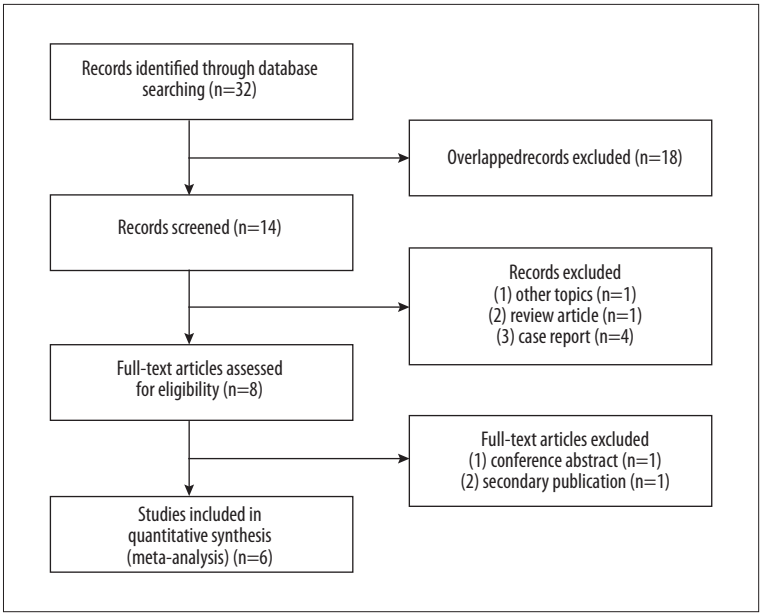

Figure 1. Flow diagram of included studies.

Table 1. Characteristics of studies included in meta-analysis.

Author	Year	Language	Sample size (case/control)	Country	Ethnicity	Type of IA	Control source	Genotyping method	HWE
Gläsker S	2014	English	269/104	Germany	Caucasian	Mixed	Population-based	PCR-RFLP	0.022
Wu P (1)	2013	English	367/396	China	Asian	Sporadic	Hospital-based	PCR-RFLP	<0.001
Yoneyama T	2004	English	260/293	Japan	Asian	Mixed	Hospital-based	PCR-Sequencing	0.630
Zhu Y	2008	English	226/326	China	Asian	Mixed	Hospital-based	PCR-RFLP	0.383
Joo SP	2009	English	320/189	Korea	Asian	Sporadic	Hospital-based	PCR-RFLP	0.0980
Wu P (2)	2010	Chinese	100/116	China	Asian	Sporadic	Hospital-based	PCR-RFLP	0.005

IA – intracranial aneurysm; HWE – Hardy-Weinberg equilibrium; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism assay; PCR-Sequencing – polymerase chain reaction-Sequencing.

were performed to explore the impact of the following: confounding factors: ethnicity, IA type and HWE. Sensitivity analysis was conducted by excluding each study one by one to challenge the robustness of pooling results. We used Begg's and Egger's tests to estimate possible publication bias [17]. All statistical analysis was performed using Stata software for Windows version 12.0 (Stata corporation, college station, TX, USA). $P<0.05$ was considered statistically significant.

Results

Study characteristics

Figure 1 summarizes the process of the literature search in a PRISMA flow diagram. Initially, a total of 32 relevant records were identified. After excluding overlapping and non-relevant records, we retrieved the full text of 8 studies for further evaluation. Two articles were further excluded for being a conference abstract or secondary publication [18,19]. Ultimately, 6 studies were included in this meta-analysis [14–16,20–22].

The study characteristics are shown in Table 1. These studies were published between 2004 and 2014, included 1542 IA patients and 1424 controls, and were conducted in Asia (3 in China, one in Japan, and one in Korea) and Europe (one in Germany). The study by Gläsker S et al. was conducted with Caucasians [20]. Among the 5 Asian studies that were included in our meta-analysis, the study by Joo SP et al. was conducted in a Korean population [16]. All subjects in the study by Yoneyama T et al. were Japanese Yamato people [14]. The study by Zhu Y et al. included Chinese Han people [15]. Participants

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 2. Quantitative analyses of COL1A2 rs42524 polymorphism and IA risk.

Variable	N	Allelic contrast		Homozygote contrast		Heterozygote contrast		Dominant model		Recessive model	
		OR (95%CI)	P_{het}	OR (95%CI)	P_{het}	OR (95%CI)	P_{het}	OR (95%CI)	P_{het}	OR (95%CI)	P_{het}
Total	6	1.74 (1.34,2.26)	0.078	1.15 (0.55–2.38)	0.415	1.81 (1.37–2.41)	0.529	1.74 (1.28–2.36)	0.328	1.76 (1.02–3.04)	0.066
Ethnicity											
Asian	5	1.88 (1.44–2.46)	0.16	1.97 (0.57–6.88)	0.424	1.82 (1.28–2.58)	0.387	1.83 (1.18–2.84)	0.232	2.42 (1.86–3.16)	0.553
Caucasian	1	1.29 (0.87–1.90)	NA	0.86 (0.35–2.13)	NA	1.81 (1.08–3.02)	NA	1.58 (0.99–2.55)	NA	0.71 (0.29–1.73)	NA
IA type											
Mixed	3	1.77 (1.16–2.68)	0.13	1.02 (0.44–2.37)	0.317	2.08 (1.50–2.89)	0.668	1.96 (1.43–2.68)	0.423	0.91 (0.32–2.58)	0.281
Sporadic	3	1.71 (1.13–2.58)	0.062	1.89 (0.33–10.69)	0.269	1.20 (0.68–2.11)	0.742	1.18 (0.69–2.04)	0.445	2.41 (1.81–3.20)	0.355
HWE											
No	3	1.78 (1.29–2.45)	0.121	1.64 (0.40–6.65)	0.247	1.84 (1.11–3.03)	0.891	1.66 (1.04–2.64)	0.625	1.85 (1.01–3.38)	0.03
Yes	3	1.70 (0.99–2.90)	0.063	1.18 (0.23–6.12)	0.283	1.80 (1.11–2.91)	0.142	1.77 (1.05–2.99)	0.091	1.11 (0.23–5.25)	0.308

OR – odds ratio; CI – confidence interval; P_{het} – P value of heterogeneity; NA – not available; IA – intracranial aneurysm; HWE – Hardy-Weinberg equilibrium.

in the other 2 studies by Wu P et al. were all Chinese people from northeast China [21,22]. All the participants who were enrolled in the aforementioned Asian studies were of Asian ethnicity. Of these studies, 3 investigated sporadic IA only, whereas the other 3 focused on both sporadic IA and familial IA. Five studies included hospital-based controls, while one study included population-based controls. The genotype distributions of the controls were in accordance with HWE, with the exception of 3 studies.

Meta-analysis results

The pooled results of the relationship between COL1A2 rs42524 polymorphism and IA risk were summarized in Table 2 and Figure 2. Overall, significant association was detected under 4 genetic models (C *vs.* G: OR=1.74, 95%CI=1.34–2.26; GC *vs.* GG: OR=1.81, 95%CI=1.37–2.41; CC+GC *vs.* GG: OR=1.74, 95%CI=1.28–2.36; CC *vs.* GC+GG: OR=1.76, 95%CI=1.02–3.04). There was significant heterogeneity among studies only in allelic model (P_{het}=0.078) and recessive model (P_{het}=0.066). To explore sources of between-study heterogeneity, we conducted subgroup analyses under all genetic models stratified by potential confounding factors. As is shown in Table 2, the association between COL1A2 rs42524 polymorphism and IA risk was still robust when stratified by ethnicity, IA type, or HWE. What's more, we found the association between COL1A2 rs42524 polymorphism and risk of IA was more strong under all 5 genetic models in Asian (C *vs.* G: OR=1.88, 95%CI=1.44–2.46; CC *vs.* GG: OR=1.97, 95%CI=0.57–6.88; GC *vs.* GG: OR=1.82, 95%CI=1.28–2.58; CC+GC *vs.* GG: OR=1.83, 95%CI=1.18–2.84; CC *vs.* GC+GG: OR=2.42, 95%CI=1.86–3.16) than in Caucasians (C *vs.* G: OR=1.29, 95%CI=0.87–1.90; CC *vs.* GG: OR=0.86, 95%CI=0.35–2.13; GC *vs.* GG: OR=1.81, 95%CI=1.08–3.02; CC+GC *vs.* GG: OR=1.58, 95%CI=0.99–2.55; CC *vs.* GC+GG: OR=0.71, 95%CI=0.29–1.73). During sensitivity analysis, we got almost the same results when excluding each study each time (data not shown). Our sensitivity analysis indicated that no individual study had significant influence on the overall conclusions.

Publication bias

The Begg's funnel plot seemed symmetrical (Figure 3). Furthermore, Egger's test didn't find any evidence for publication bias (C *vs.* G: p=0.694).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

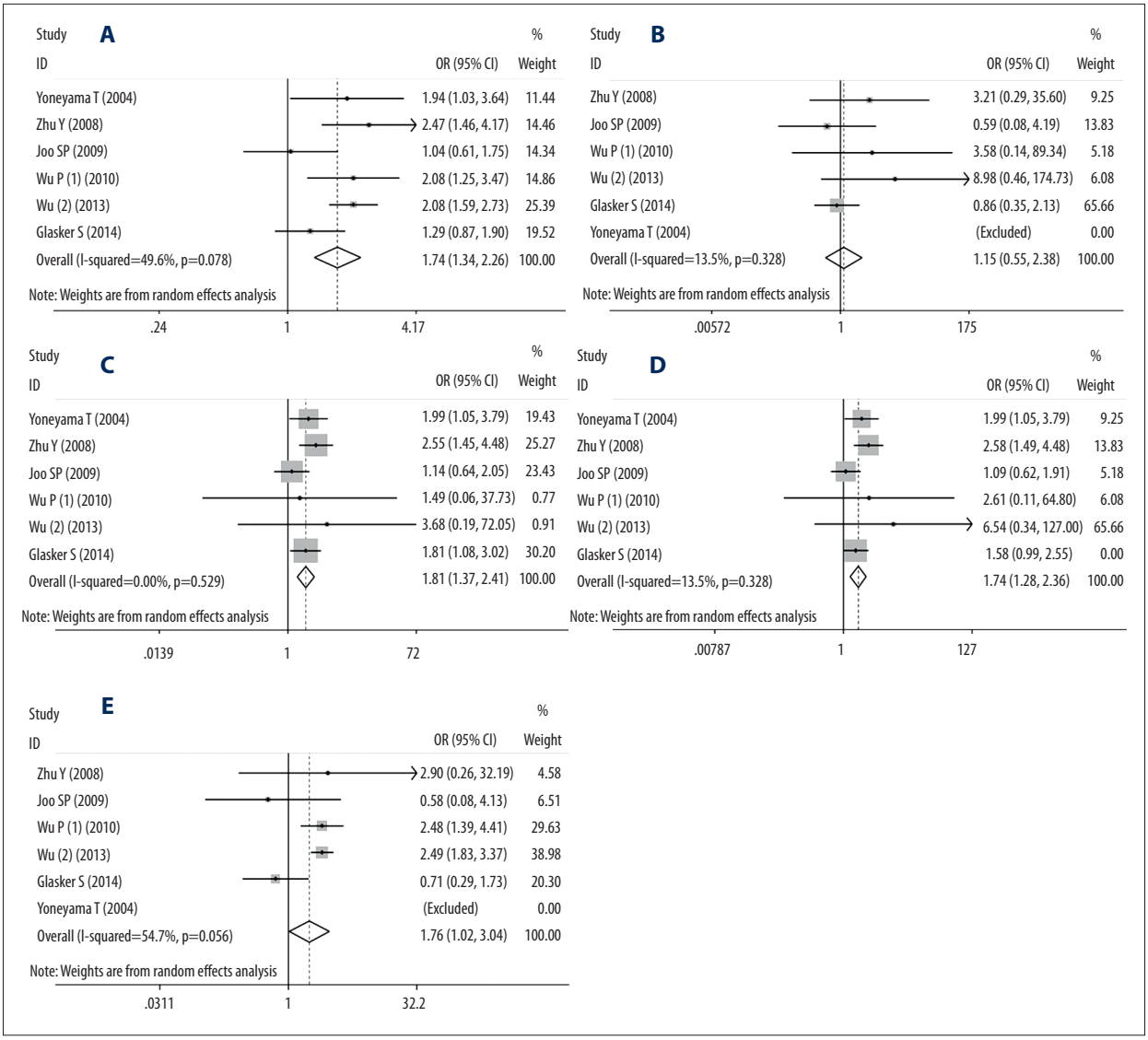

Figure 2. Forest plot for the association between collagen type I alpha2 rs42524 polymorphism with intracranial aneurysm risk. (**A**) forest plot for allelic contrast (C *vs.* G); (**B**) forest plot for homozygote contrast (CC *vs.* GG); (**C**) forest plot for heterozygote contrast (GC *vs.* GG); (**D**) forest plot for dominant model (CC + GC *vs.* GG); (**E**) forest plot for recessive model (CC *vs.* GC +GG).

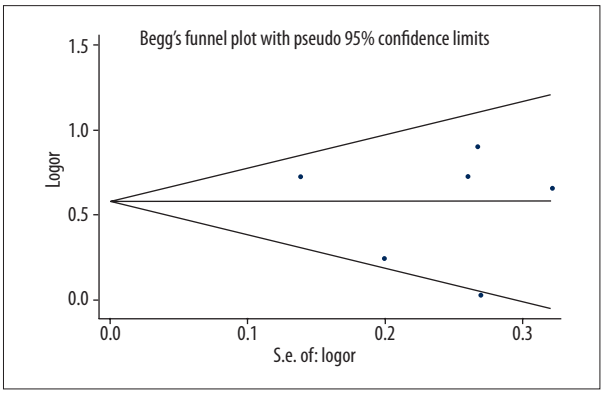

Figure 3. The funnel plots assessing publication bias (C *vs.* G).

Discussion

There are 19 different types of collagen within the collagen protein family. Among them, type I collagen and type III collagen represent 80% to 90% of total arterial collagen and contribute the most to arterial tensile strength [23]. The cerebral artery is mainly composed of 3 histologic layers, including the inner intima, muscular media and outer collagenous adventitia. A lack of external elastic lamina in intracranial arteries compared with extracranial arteries make it susceptible to aneurysm if the collagen is defective, especially at bifurcations where the smooth muscle cell layer and the internal elastic lamina are more likely to be defective [24,25]. Thus, there is a sufficient theoretical basis that COL1A2, which encodes the

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

alpha 2 chain of type I collagen, is a candidate gene to explain IA risk. In the present meta-analysis, we demonstrated a significant risk effect of the C allele of rs42524 in COL1A2 on IA susceptibility using 4 genetic models.

Our subgroup analysis, which was stratified by ethnicity, showed a significantly increased IA risk in people carrying the C allele of rs42524 in COL1A2 in both Asian and Caucasian subgroups. However, the association between COL1A2 rs42524 polymorphism and risk of IA was stronger in Asians than in Caucasians, which may be partially due to the differences in the frequencies of genetic polymorphisms in the different ethnic groups. Interestingly, Gläsker et al. detected a significant association between IA and rs42524 [20]. However, research from Korea (Joo et al.) indicated that genotype frequencies of the rs42524 polymorphism were similar in patients with IA and controls, which suggests that this polymorphism is not associated with IA in the Korean population [16]. The divergent results may be because the observed polymorphic sequence might be influenced by different genetic and environmental backgrounds in different ethnic groups. It is also possible that this polymorphism might not be related to the pathogenesis of IA. For these reasons, larger-scale original studies of different ethnic groups are needed. As shown in our research, the frequencies of C in the COL1A2 rs42524 polymorphism varied from 5.19% to 87.06%. As IA is considered to be a multigenic disease, different pathogeneses involved in IA may also contribute to the variety of results across different population. We also performed subgroup analyses according to IA type and HWE results and obtained similar results in different subgroups, which indicates that our pooled result may not be obviously confounded by different IA types in the case group. Furthermore, our results were robust and reliable, despite the inclusion of studies that did not meet HWE.

Several studies have investigated the potential functional effects of rs42524. As this SNP is located in exon 28 of COL1A2, variation at this site would lead to an Ala to Pro substitution at amino acid residue 459, which is in the Gly-X-Y repeat of the triple-helical domain of type I collagen. Using circular dichroism spectra, Yoneyama et al. showed that the Pro-549 peptide had higher thermal stability than the Ala-549 peptide and speculated that it affected the rigidity or elasticity of the vascular wall [14]. In addition, as a key structural component of broad tissue, type I collagen can also interact with various molecules and cells, performing numerous physiological functions. As a result, local conformational change due to the amino acid change from the rs42524 polymorphism could affect the interaction of type I collagen with other molecules, eventually weakening the vascular wall and leading to susceptibility to IA [26].

Some limitations should also be addressed when interpreting the results of this meta-analysis. First, as a complex disease, IA is influenced by multiple factors, including genetic and environmental factors. However, as limited information was provided in most of the studies, we could not provide an adjusted result that considered all the confounding factors. Additionally, we could not further explore gene-gene or gene-environment interactions or the interactions of different polymorphic *loci* in this research. Second, the sample sizes of some of the subgroups in our meta-analysis were relatively small, which reduces the representativeness of the population. More studies, especially those with different ethnic populations, are needed to validate our results. Third, some of the included studies were not consistent with HWE, which may have biased the pooled results. However, our results did not change after excluding these studies in the sensitivity analysis.

Conclusions

Our meta-analysis suggests that COL1A2 rs42524 is a significant risk factor for IA susceptibility, with an especially strong effect in Asian people. The COL1A2 rs42524 polymorphism could increase the risk of IA, regardless of ethnicity, HWE, and IA type. More data from research conducted with different ethnic populations are still needed to confirm our findings.

Conflict of interest

The authors have declared no conflicts of interest.

References:

1. Farnham JM, Camp NJ, Neuhausen SL et al: Confirmation of chromosome 7q11 locus for predisposition to intracranial aneurysm. Hum Genet, 2004; 114: 250–55
2. Iwamoto H, Kiyohara Y, Fujishima M et al: Prevalence of intracranial saccular aneurysms in a Japanese community based on a consecutive autopsy series during a 30-year observation period. The Hisayama study. Stroke, 1999; 30: 1390–95
3. Nakagawa T, Hashi K: The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. J Neurosurg, 1994; 80: 217–23
4. Hop JW, Rinkel GJ, Algra A, van Gijn J: Case-fatality rates and functional outcome after subarachnoid hemorrhage: A systematic review. Stroke, 1997; 28: 660–64
5. Visser-Meily JM, Rhebergen ML, Rinkel GJ, van Zandvoort MJ, Post MW: Long-term health-related quality of life after aneurysmal subarachnoid hemorrhage: relationship with psychological symptoms and personality characteristics. Stroke, 2009; 40: 1526–29
6. Rinkel GJ: Intracranial aneurysm screening: indications and advice for practice. Lancet Neurol, 2005; 4: 122–28
7. Ronkainen A, Hernesniemi J, Puranen M et al: Familial intracranial aneurysms. Lancet, 1997; 349: 380–84
8. Schievink WI, Schaid DJ, Michels VV, Piepgras DG: Familial aneurysmal subarachnoid hemorrhage: a community-based study. J Neurosurg, 1995; 83: 426–29

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

9. Schievink WI: Genetics of intracranial aneurysms. Neurosurgery, 1997; 40: 651–62; discussion 662–63
10. Vaicys C, Hunt CD, Heary RF: Ruptured intracranial aneurysm in an adolescent with Alport's syndrome – a new expression of type IV collagenopathy: Case report. Surg Neurol, 2000; 54: 68–72
11. Krischek B, Inoue I: The genetics of intracranial aneurysms. J Hum Genet, 2006; 51: 587–94
12. Peters DG, Kassam AB, Feingold E et al: Molecular anatomy of an intracranial aneurysm: coordinated expression of genes involved in wound healing and tissue remodeling. Stroke, 2001; 32: 1036–42
13. Onda H, Kasuya H, Yoneyama T et al: Genomewide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. Am J Hum Genet, 2001; 69: 804–19
14. Yoneyama T, Kasuya H, Onda H et al: Collagen type I alpha2 (COL1A2) is the susceptible gene for intracranial aneurysms. Stroke, 2004; 35: 443–48
15. Zhu Y, Li W, Ge M et al: Polymorphism rs42524 of COL1A2 and sporadic intracranial aneurysms in the Chinese population. J Neurosurg, 2008; 109: 1060–64
16. Joo SP, Kim TS, Lee IK et al: The role of collagen type I alpha2 polymorphisms: Intracranial aneurysms in Koreans. Surg Neurol, 2009; 72: 48–53
17. Egger M, Smith GD, Phillips AN: Meta-analysis: principles and procedures. BMJ, 1997; 315: 1533–37
18. Zhu Y, Wang X, He H et al: [Detection and analysis of the polymorphism of rs42524 of type I collagen alpha2 gene in intracranial aneurysms]. Chin J Neurosurg, 2009; 25: 1118–21
19. Sanish S, Linda K, Shabeesh B et al: The role of versican and collagen type I ALPHA2 polymorphisms in intracranial aneurysms in a South Indian Population. HUGO Journal, 2011; 1: 206–7
20. Glasker S, Schatlo B, Klingler JH et al: Associations of collagen type I alpha2 polymorphisms with the presence of intracranial aneurysms in patients from Germany. J Stroke Cerebrovasc Dis, 2014; 23: 356–60
21. Wu P, Li B, Wu A,Wang Y: Is type I alpha 2 collagen gene responsible for intracranial aneurysm in Northeast China? Neural Regen Res, 2013; 8: 445–51
22. Wu P, Pan Q, Wu A, Wang Y: [The correlations of COLlA2 gene polymorphism and sporadic intracranial aneurysm in Chinese people]. Shangdong Medicine Journal, 2010; 50: 61–62 [in Chinese]
23. Stehbens W: Pathology of the cerebral blood vessels. W. St Louis (Mo): Mosby, 1972
24. Fujimoto K: 'Medial defects' in the prenatal human cerebral arteries: an electron microscopic study. Stroke, 1996; 27: 706–8
25. Stehbens WE: Aetiology of cerebral aneurysms. Lancet, 1981; 2: 524–25
26. Leikina E, Mertts MV, Kuznetsova N, Leikin S: Type I collagen is thermally unstable at body temperature. Proc Natl Acad Sci USA, 2002; 99: 1314–18

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]