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REVIEW

The association between collagen gene polymorphisms and intracranial aneurysms: a meta-analysis

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Abstract The association between single nucleotide polymorphisms (SNPs) of the collagen gene and intracranial aneurysm (IA) pathogenesis remains controversial. Thus, in this study, a meta-analysis was performed to evaluate the association between collagen gene SNPs and the incidence of IA. A systematic search of major online databases up to March 2017 was performed. Five genetic models (allelic, dominant, recessive, heterozygous, and homozygous models) were used to analyze the associations. A total of 14 trials with 13,709 patients were included. Four collagen genes, COL1A2 (21 SNPs), COL3A1 (7 SNPs), COL4A1 (6 SNPs), and COL4A2 (1 SNP), were analyzed. We observed that rs42524 in the COL1A2 gene was associated with a significant increase in the risk of IA in Japanese patients (allelic model: OR, 1.94; 95% CI, 1.03–3.64; $p = 0.04$); the rs1800255 polymorphism in the COL3A1 gene was significantly correlated with Chinese IA patients (allelic model: OR, 1.50; 95% CI, 1.30–1.73; $p < 0.001$); and rs2621215 was significantly correlated with IA for the heterozygous model (OR, 1.58; 95% CI, 1.15–2.17; $p = 0.005$) and the dominant model (OR, 1.49; 95% CI, 1.09–2.02; $p = 0.012$). Furthermore, in the COL4A1 gene, there was a significant relationship between the rs3783107 polymorphism and a Dutch IA population (allelic model: OR, 1.23; 95% CI, 1.06–1.42; $p = 0.006$), and the prevalence ratio of mutation carriers in the Dutch population was significantly higher than that in the Japanese population (ROR, 1.31; 95% CI, 1.07–1.63; $p = 0.008$). The rs1800255 polymorphism in COL3A1 is robustly correlated with IA in the Chinese population. Three COL1A2 SNPs—rs42524, rs1800238, and rs2621215—should be studied further.

Keywords Intracranial aneurysm · Collagen · Single nucleotide polymorphism · Meta-analysis

Introduction

The incidence of intracranial aneurysm (IA) in the non-risk population is approximately 2–3%, and this proportion gradually increases with age [1, 2]. Subarachnoid hemorrhage (SAH) caused by IA is an important subtype of stroke with a high morbidity and mortality and is a major public health problem because of its sudden and severe occurrence, unexpected onset, and lack of warning signs. The rate of fatality of aneurysmal SAH is approximately 50%, and 20% of those who survive require care to be provided by others [3]. The International Study of Unruptured Intracranial Aneurysms Investigators (ISUIA) also recommended that early screening and prophylactic treatment for patients with no history of IA rupture can significantly improve prognosis [4]. Therefore, it is important to analyze the IA risk factors for early detection of asymptomatic unruptured aneurysms.

The pathogenesis of IA was still unclear, but it is generally believed that IA is derived from the degeneration of long-term blood flow. However, the characteristics of family aggregation also suggest that genetic factors play an important role in onset. Therefore, it is widely considered a complex disease caused by polygenic inheritance, hemodynamic effects, and

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acquired degeneration. Systematic reviews have previously analyzed the relationship between single nucleotide polymorphisms (SNPs) and IA pathogenesis. These studies have shown that the T786C polymorphism of *endothelial nitric oxide synthase* (*eNOS*) is an important predictor of IA [5, 6]. In addition, rs1800956 of *endoglin* [7], *interleukin-6* (*IL-6*) promoter polymorphisms (-174G/C and -572G/C) [8], *angiotensin converting enzyme* (*ACE*) insertion/deletion [9], etc., have also been found to be related to IA.

The extracellular matrix (ECM) in the arterial wall provides strength and elasticity, allowing arteries to maintain their structural and functional integrity. Abnormal ECM may be a risk factor for IA [10]. The ECM is a stable macromolecular complex secreted by arterial cells that contain collagen, elastin, glycoprotein, and proteoglycan, etc., among which the major component is collagen. Collagen types I, III, IV, V, and VI are related to arterial formation, although types I and III account for 80~90% of all collagen [10]. Although collagen is the major component of connective tissue and plays an important role in maintaining arterial integrity, the collection of SNPs of the collagen gene and IA pathogenesis remains controversial. In addition, differences among races and ethnicity might affect IA susceptibility among those with SNPs, and therefore, more studies of differences across races and countries are needed to confirm the effects of SNPs of the collagen gene. This meta-analysis was performed to confirm the hypothesis that there is an association between SNPs of the collagen gene and IA to develop preventive procedures for use in IA screening. In this study, a case-control study was conducted. IA patients and hospitalized non-IA patients were enrolled in the same period. The two groups were matched for factors such as sex, residence, and age. The exposure factors were different SNPs of the collagen gene, and the outcome indicator was the allelic frequencies of the individual genotypes in the IA patients and controls.

Methods

We used the meta-analysis of observational studies in epidemiology (MOOSE) guideline.

Data sources and search strategy

A literature search was independently performed by two researchers across public electronic databases including Medline, Embase, and Cochrane Library and Chinese databases including the China National Knowledge Infrastructure (CNKI), China Science Periodical Database (CSPD, Wanfang Database), VIP journal integration platform (VJIP), and China Biology Medicine (CBM) database through March 2017 without language restrictions. The following search terms were used: "intracranial aneurysm," "cerebral aneurysm," "brain aneurysm" and "collagen." We also conducted manual searches of reference lists from all the relevant original and review articles to identify additional eligible studies.

Criteria selection

Studies were included in this meta-analysis that met the following criteria: (1) case-control studies comparing IA and non-IA populations, (2) exploration of the association between collagen genetic polymorphisms and IA, and (3) studies reporting allelic frequencies of individual genotypes in cases and controls. Exclusion criteria included SAH-related study, studies of other genetic disorders associated with IA, comparative studies of familial and sporadic IA, or arterial malformation-related studies, etc. Reviews, non-human studies, editorial comments, and case reports were also excluded. Additionally, non-peer-reviewed studies such as conference abstracts, dissertations, and unpublished articles were also excluded due to their lack of reliability.

Data extraction and quality assessment

Two researchers independently extracted the following information from the included studies: author, publication year, sample size, population source, type of IA (family/sporadic), IA defined, test methods, and genes/SNPs. The Newcastle-Ottawa Scale (NOS), which has been validated for evaluating the quality of observational studies in meta-analyses, was used to evaluate the methodological quality of the included studies [11]. The NOS was based on the following 3 subscales: selection (4 items, 4 stars), comparability (1 item, 2 stars), and exposure (3 items, 3 stars).

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) of the included populations was calculated to assess the allele frequencies among generations. The association analysis was performed using five genetic models: allelic (W vs. M), dominant (WW + WM vs. MM), recessive (WW vs. WM + MM), heterozygous (WM vs. MM), and homozygous (WW vs. MM) models in which W represents the major wild-type allele, and M represents the minor mutant-type allele [12]. The strengths of associations were estimated by calculating the summary odds ratio (OR) and its 95% confidence interval (CI) using a random effects model. The I^2 statistic was still used to estimate the degree of heterogeneity among studies. Publication bias was assessed by visually examining the funnel plots and using the Begg-Mazumdar and Egger tests if the number of included studies was greater than 2. Funnel plots were generated if the number of included studies was greater than four. The trim

and fill method was used to correct for publication bias if necessary. In the meta-analysis, the number of false-positive errors was relatively high, especially when a small number of participants was included. Therefore, we used trial sequential analysis (TSA) to identify whether the results were robust and conclusive. The TSA was conducted to maintain a type I error of 5% and a power of 80%. The information size was also calculated using the estimates of the effect size of trials [13]. For each country, we extracted the race-specific ORs (with 95% CIs) for whether individuals have a potential risk of SNPs, from which we estimated the race-to-race ORs (RORs) and the corresponding 95% CIs [14]. All tests were two-tailed, and a p value of less than 0.05 was considered statistically significant. We analyzed the data using Review Manager (Version 5.3) and STATA (Version 14.0).

Results

We identified 299 articles from English public databases after removing duplications and 443 articles from Chinese public databases. After screened the titles and abstracts, 680 of these articles were excluded. The full texts of the 52 articles were assessed, among which non-collagen gene-related SNP studies (24), non-control studies (7), non-SNP but genotype studies (3), duplicated publications (2), and studies including patients with other diseases (2) were excluded. Finally, 14 trials

Table 1 Characters of the included studies

Author	Year	Sample size	Population source	Type of IA	IA defined	Test methods	Genes/SNPs	NOS score
Ge Mingxu [15]	2008	214	China	Sporadic	CT/DSA/MRA/surgery	PCR	*COL3A1*/rs1800255	7
Hua Tao [16]	2008	113	China	Sporadic	DSA/surgery	PCR	*COL3A1*/rs1800255, rs1516446, rs2271683, nt2346	7
Pengfei Wu [17]	2013	763	China	Sporadic	CT/DSA/MRA/surgery	PCR	*COL1A2*/rs42524	8
Sven Glasker [18]	2014	373	Germany	Both	NA	PCR	*COL1A2*/rs42524, rs1800238, rs2621215	7
Femke N.G. [19]	2013	3401	Dutch	Both	CA/CTA/MRA	Gene chip analysis	*COL4A2*/rs4773144	6
Jinzhou Chen [20]	2012	786	China	Sporadic	CT/DSA/MRA/surgery	PCR	*COL3A1*/rs2138533, rs11887092, rs1800255	7
		1882	China	Sporadic	CT/DSA/MRA/surgery	PCR	*COL3A1*/rs2138533, rs11887092, rs1800255	
Sungpil Joo [21]	2009	509	Korea	Sporadic	CT/DSA/MRA	PCR	*COL1A2*/rs42524, rs2621215	8
Ynte M. Ruigrok [22]	2009	1440	Japan	Both	MRI	TaqMan assays	*COL4A1*/rs3783107	6
Yufang Zhu [23]	2008	552	China	Sporadic	CT/MRA/surgery	PCR	*COL1A2*/rs42524	8
Yute M. Ruigrok [24]	2006	972	Dutch	Both	CT/MRA	GoldenGate assay	*COL4A1*/rs12017058, rs3783107, rs675605, rs630943, rs2391824	6
		646	Dutch	Both	CT/MRA	TaqMan sssays	*COL4A1*/rs12017058, rs3783107, rs675605, rs630943, rs2391824	6
Taku Yoneyama [25]	2004	553	Japan	Both	CT/MRA/surgery	PCR	*COL1A2*/21 SNPs[a]	8
Zhu Yufang [26]	2009	786	China	Both	CT/MRI	PCR	*COL3A1*/rs2138533, rs11887092, rs1040186	7
Wu Pengfei [27]	2010	216	China	Sporadic	CTA/MRA/surgery	PCR	*COL1A2*/rs42524	7
Zhu Yufang [28]	2009	503	China	Both	CTA/DSA/MRA/surgery	PCR	*COL3A1*/rs1800255	7

CA conventional angiography, *CT/CTA* computed tomography/computed tomography angiography, *DSA* digital subtraction angiography, *IA* intracranial aneurysm, *MRI/MRA* magnetic resonance angiography, *NA* not available, *NOS* Newcastle-Ottawa scale, *PCR* polymerase chain reaction, *SNP* single nucleotide polymorphism

[a] rs1060399, rs1800222, rs1800248, rs1801182, rs2299417, rs2521206, rs369982, rs388625, rs389328, rs400218, rs412777, rs421587, rs42517, rs42526, rs42527, rs42530, rs435184, rs62464631, rs42524, rs1800238, rs2621215

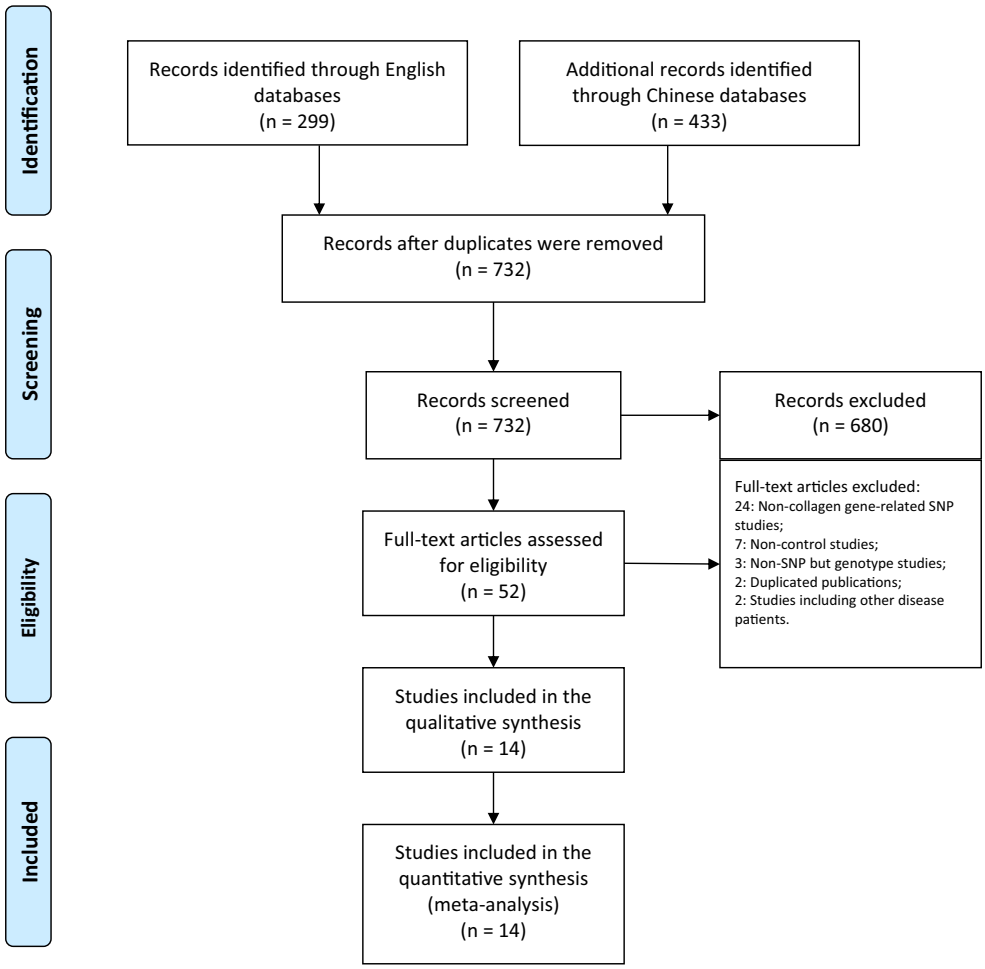


Fig. 1 PRISMA flowchart illustrating the selection process of studies included in our analysis

assessing 13,709 patients were included in our meta-analysis (Table 1, Fig. 1) [15–28].

In this study, five Chinese articles [15, 16, 26–28] and nine English articles [17–25] were included that were published from 2004–2014. The included studies corresponded to the following countries: China, Germany, Dutch, Korea, and Japan. The IA confirming methods included computed tomography angiography (CTA), magnetic resonance angiography (MRA), digital subtraction angiography (DSA), conventional angiography (CA), and surgery. These methods were ideal for detecting the presence of IA in patients. The methods of the SNP genotype analysis included polymerase chain reaction (PCR), gene chip analysis, TaqMan assays, and GoldenGate assays. All reported SNPs had been verified by the National Center for Biotechnology Information (NCBI) database query that are present and unique (Table 1).

Because of the limited number of studies, it was impossible to separate familial and sporadic IA. In addition, in large-scale studies, it was also difficult to distinguish whether the patient was diagnosed with familial or sporadic IA. Therefore, our study did not consider the difference between the two types of IA in SNPs. *COL1A2* (21SNPs), *COL3A1* (7SNPs), *COL4A1* (6SNPs), and *COL4A2* (1SNP) genes were included in our study. According to the NOS quality analysis, five studies received a score of 8, seven studies received a score of 7, and four studies received a score of 6 (Table 1). The main factors influencing the quality of the studies included 1) the choice of the control group regarding whether a healthy population was included or another patient population without clearly explaining the source, 2) the comparability of the study regarding whether the impact of confounding factors was considered, and 3) the determination of exposure not described in detail in the article. The above bias factors need to be carefully considered in further study designs. Overall, the quality of the included studies was ideal.

In the *COL1A2* gene, 21 SNPs were analyzed. Eighteen of the SNPs came from a single Japanese population study [25] and showed no significant association with IA incidence. In rs42524-related studies, the polymorphism of this loci significant increased the risk of IA based on one Japanese population study (allelic model: OR, 1.94; 95% CI, 1.03–3.64; $p = 0.04$) [25]. However, there were contrary results concerning with high heterogeneity ($I^2 = 95.5\%$) among the three Chinese population-based studies without a significant

Table 2 Meta-analysis of the association between SNPs and IA

Gene	Countries	SNPs/HWE test	Model	No. of study	OR	LCI	UCI	P value	I^2	Begg	Egger
COL1A2	Japan	rs1060399	Allelic model	1	1.33	0.89	1.99	0.17	*	*	*
	Japan	rs1800222	Allelic model	1	0.87	0.74	1.03	0.10	*	*	*
	Japan	rs1800248	Allelic model	1	0.94	0.69	1.27	0.69	*	*	*
	Japan	rs1801182	Allelic model	1	0.83	0.68	1.01	0.07	*	*	*
	Japan	rs2299417	Allelic model	1	1.05	0.66	1.66	0.85	*	*	*
	Japan	rs2521206	Allelic model	1	1.16	0.99	1.36	0.07	*	*	*
	Japan	rs369982	Allelic model	1	1.10	0.88	1.38	0.40	*	*	*
	Japan	rs388625	Allelic model	1	1.00	0.86	1.16	0.96	*	*	*
	Japan	rs389328	Allelic model	1	2.78	0.54	14.22	0.22	*	*	*
	Japan	rs400218	Allelic model	1	1.08	0.93	1.26	0.33	*	*	*
	Japan	rs412777	Allelic model	1	1.14	0.93	1.40	0.21	*	*	*
	Japan	rs421587	Allelic model	1	1.03	0.82	1.30	0.79	*	*	*
	Japan	rs42517	Allelic model	1	1.18	0.92	1.52	0.20	*	*	*
	Japan	rs42526	Allelic model	1	0.90	0.76	1.08	0.27	*	*	*
	Japan	rs42527	Allelic model	1	1.18	0.91	1.53	0.22	*	*	*
	Japan	rs42530	Allelic model	1	1.26	0.97	1.64	0.08	*	*	*
	Japan	rs435184	Allelic model	1	1.15	0.93	1.43	0.19	*	*	*
	Japan	rs62464631	Allelic model	1	0.94	0.68	1.30	0.73	*	*	*
	China/Japan/Korean/Germany	rs42524	Allelic model	6	1.33	0.74	2.42	0.34	90.6%	0.452	**0.017**
		HWE test	Heterozygous model	6	1.32	0.61	2.87	0.48	90.4%	1	0.217
		Case: < 0.001	Homozygous model	5	0.88	0.42	1.83	0.73	0%	1	0.935
		Control:< 0.001	Dominant model	6	1.31	0.61	2.79	0.49	90.5%	1	0.204
		Total:< 0.001	Recessive model	5	1.12	0.45	2.81	0.80	56.1%	0.806	0.297
	China		Allelic model	3	1.33	0.41	4.27	0.63	95.5%	0.296	**0.024**
	Germany		Allelic model	1	1.29	0.87	1.90	0.21	*	*	*
	Korea		Allelic model	1	1.04	0.61	1.76	0.90	*	*	*
	Japan[a]		**Allelic model**	**1**	**1.94**	**1.03**	**3.64**	**0.04**	*	*	*
	Japan/Germany	**rs1800238**	**Allelic model**	**2**	**0.73**	**0.57**	**0.94**	**0.01**	0%	1	*
		HWE test	**Heterozygous model**	**2**	**0.59**	**0.41**	**0.38**	**0.00**	0%	1	*
		Case: < 0.001	Homozygous Model	1	0.65	0.39	1.09	0.10	*	*	*
		Control:0.147	**Dominant model**	**2**	**0.60**	**0.43**	**0.84**	**0.00**	0%	1	*
		Total:< 0.001	Recessive model	1	0.86	0.53	1.39	0.53	*	*	*
	Japan		**Allelic model**	**1**	**0.74**	**0.58**	**0.94**	**0.02**	*	*	*
	Germany		Allelic model	1	0.58	0.11	3.18	0.53	*	*	*
	Japan/Korean/Germany	rs2621215	Allelic model	3	1.35	0.92	1.99	0.13	45.1%	1	0.637
		HWE test	**Heterozygous model**	**3**	**1.58**	**1.15**	**2.17**	**0.01**	0%	0.296	0.533
		Case:0.731	Homozygous model	2	0.61	0.25	1.53	0.30	0%	1	*
		Control:0.012	**Dominant model**	**3**	**1.49**	**1.09**	**2.02**	**0.01**	1.4%	1	0.968
		Total:0.049	Recessive model	2	0.55	0.22	1.36	0.20	0%	1	*
	Korea		Allelic model	1	1.03	0.69	1.53	0.90	*	*	*
	Germany		Allelic model	1	1.35	0.73	2.51	0.34	*	*	*
	Japan		**Allelic model**	**1**	**1.90**	**1.16**	**3.12**	**0.01**	*	*	*
COL3A1	China	**rs1800255**	**Allelic model**	**5**	**1.50**	**1.30**	**1.73**	**0.00**	0%	0.221	0.289
		HWE test	**Heterozygous model**	**5**	**1.68**	**1.40**	**2.00**	**0.00**	0%	0.462	0.514
		Case:0.204	**Homozygous model**	**5**	**1.67**	**1.11**	**2.51**	**0.01**	0%	0.221	0.174
		Control:0.753	**Dominant model**	**5**	**1.68**	**1.41**	**1.99**	**0.00**	0%	0.462	0.431
		Total:0.796	Recessive model	5	1.40	0.94	2.08	0.10	0%	0.462	0.148

Table 2 (continued)

Gene	Countries	SNPs/HWE test	Model	No. of study	OR	LCI	UCI	P value	I^2	Begg	Egger
	China	rs11887092	Allelic model	3	1.04	0.87	1.25	0.64	0%	0.602	*
		HWE test	Heterozygous model	3	1.03	0.84	1.27	0.75	0%	0.602	*
		Case:0.744	Homozygous model	3	1.16	0.59	2.28	0.67	0%	0.602	*
		Control:0.706	Dominant model	3	1.04	0.85	1.27	0.69	0%	0.602	*
		Total:0.624	Recessive model	3	1.15	0.58	2.26	0.69	0%	0.602	*
	China	rs2138533	Allelic model	3	0.82	0.51	1.30	0.40	92.1%	0.296	0.124
		HWE test	Heterozygous model	3	0.91	0.51	1.65	0.77	90.4%	1	0.797
		Case:0.733	Homozygous model	3	0.63	0.28	1.39	0.25	83.2%	0.296	0.057
		Control:0.171	Dominant model	3	0.85	0.46	1.59	0.62	92.1%	1	0.952
		Total:0.236	Recessive model	3	0.65	0.36	1.15	0.14	71.6%	0.296	**0.018**
	China	rs1516446	Allelic model	1	*	*	*	*	*	*	*
	China	rs2271683	Allelic model	1	3.17	0.63	16.05	0.16	*	*	*
	China	nt2346	Allelic model	1	1.34	0.48	3.72	0.58	*	*	*
	China	rs1040186	Allelic model	1	0.90	0.73	1.11	0.32	*	*	*
COL4A1	Dutch/Japan	rs3783107	Allelic model	3	1.10	0.89	1.36	0.37	73.9%	1	0.488
	Dutch		Allelic model	**2**	**1.23**	**1.06**	**1.42**	**0.01**	0	1	*
	Japan		Allelic model	1	0.93	0.80	1.08	0.33	*	*	*
	Dutch	rs9588107	Allelic model	2	1.12	0.89	1.42	0.34	63.8%	1	*
	Dutch	rs675605	Allelic model	2	1.09	0.84	1.42	0.52	64.6%	1	*
	Dutch	rs630943	Allelic model	2	1.11	0.84	1.47	0.48	67.8%	1	*
	Dutch	rs2391824	Allelic model	2	1.16	0.96	1.40	0.14	40.9%	1	*
	Dutch	rs12017058	Allelic model	2	1.13	0.98	1.30	0.09	*	1	*
COL4A2	Dutch	rs4773144	Allelic model	1	1.09	*	*	0.23	*	*	*

COL1A2 collagen type I alpha 2, *COL3A1* collagen type III alpha 1, *COL4A1* collagen type IV alpha 1, *COL4A2* collagen type IV alpha 2, *HWE* Hardy-Weinberg equilibrium, *LCI* lower confidence intervals, *OR* odds ratio, *SNP* single nucleotide polymorphism, *UCI* upper confidence interval

[a] Bold characters in the table indicate that the *p* value is less than 0.05

[*] Not evaluated

relationship between loci and IA in pool (allelic model: OR, 1.33; 95% CI, 0.414–4.272; $p = 0.632$) [17, 23, 27]. Overall, the results of rs42524 also did not show a significant relationship (allelic model: OR, 1.334; 95% CI, 0.736–2.416; $p = 0.342$) (Table 2) [17, 18, 21, 23, 25, 27]. Publication bias was found in the allelic model of rs42524 based on Egger's test ($p = 0.017$) but not Begg's test ($p = 0.452$). After correction using the trim and fill method, the random effect model results were unchanged (allelic model: OR, 0.76; 95% CI, 0.416–1.373; $p = 0.357$). In the Chinese population-based studies, publication bias was found using Egger's test ($p = 0.024$), and the results were unchanged after correction (OR, 0.48; 95% CI, 0.15–1.56; $p = 0.222$) (Table 2).

There was a negative association between rs1800238 polymorphism and IA based on two studies (allelic model: OR, 0.73; 95% CI, 0.57–0.94; $p = 0.013$) (Table 2) [18, 25]. TSA showed that the cumulative z-curve crossed the trial sequential monitoring boundary when the relative risk reduction (RRR) was 15%; however, the low number of studies may limit the reliability of this result. In addition, the association between rs1800238 and IA should be further studied (Fig. 2a).

Three studies considered the association of rs2621215 and IA, and only the heterozygous model (OR, 1.58; 95% CI, 1.15–2.17; $p = 0.005$) and dominant model (OR, 1.49; 95% CI, 1.09–2.02; $p = 0.012$), but not allelic model (OR, 1.35; 95% CI, 0.92–1.99; $p = 0.127$), revealed a significant association [18, 21, 25]. This may indicate that heterozygote carriers have higher weights on the association results (Table 2). TSA also showed that the cumulative z-curve did not cross the trial sequential monitoring boundary or even the conventional test boundary ($z = 1.96$) (Fig. 2b). It was worth noting that rs1800238 and rs2621215 are more affected by the single study and lack of robustness [25], and therefore, more related studies are needed to further confirm the association. There was no publication bias (Table 2).

Seven SNPs were analyzed in the *COL3A1* gene. The rs1800255 polymorphism was significantly correlated with Chinese IA patients (allelic model: OR, 1.50; 95% CI, 1.30–1.73; $p < 0.001$) (Table 2) [15, 16, 20, 28]. TSA showed that the cumulative z-curve crossed the trial sequential monitoring boundary, indicating that further studies are not needed and

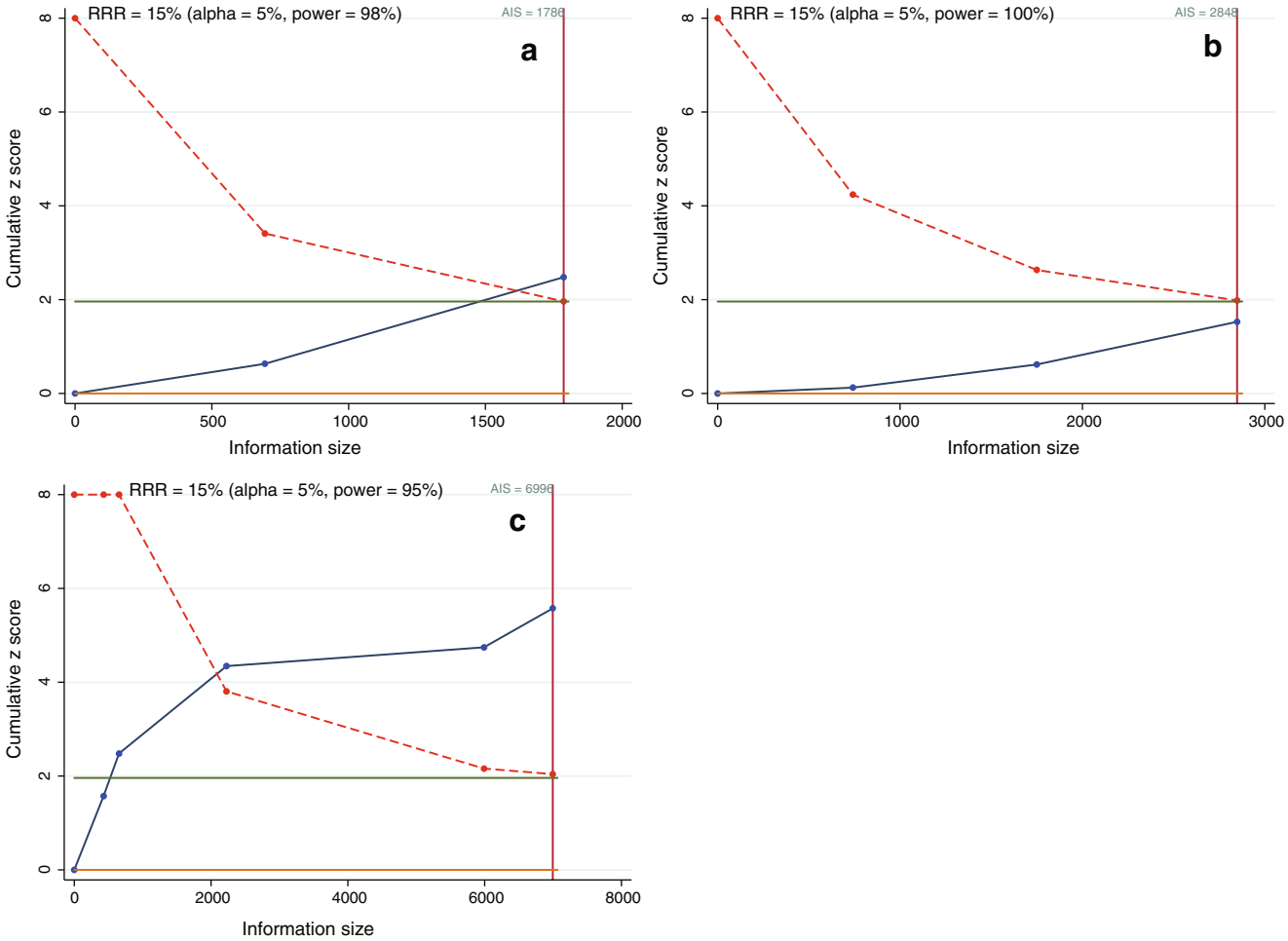


Fig. 2 Trial sequential analysis of the cumulative meta-analysis for the allelic model of COL1A2 rs1800238 (**a**), COL1A2 rs2621215 (**b**), and COL3A1 rs1800255 (**c**). The cumulative z-curve crossed the trial sequential monitoring boundary for COL1A2 rs1800238 (**a**) and COL3A1 rs1800255 (**c**) but did not cross the trial sequential monitoring boundary or even the conventional test boundary for COL1A2 rs2621215 (**b**)

are unlikely to change the conclusions (Fig. 2c). There was no significant association between the incidence of IA and other SNPs. Publication bias was found in the recessive model of rs2138533 using Egger's test ($p = 0.018$), and the results were unchanged after correction (Table 2).

Six SNPs were analyzed in the *COL4A1* gene. There was a significant relationship between rs3783107 polymorphism and Dutch IA populations (allelic model: OR, 1.23; 95% CI, 1.06–1.42; $p = 0.006$) [24] but no significant relationships with populations of other countries [22] or other SNPs of the *COL4A1* gene (Table 2) [24]. In addition, only one SNP of the *COL4A2* gene was analyzed, which was not correlated with IA (Table 2) [19]. There was no publication bias (Table 2).

Because IA incidence is still considered to be the result of multifactorial inheritance, the present study further analyzed the different risks among SNPs in different countries. The results showed that only rs3783107 polymorphism of the *COL4A1* gene was associated with a significantly higher prevalence ratio of mutation carriers in the Dutch population than in the Japanese population (ROR, 1.31; 95% CI, 1.07–1.63; $p = 0.008$). No other differences were found among other country comparisons (Fig. 3).

Discussion

In our meta-analysis, we first comprehensively analyzed four collagen-related genes. We found that rs1800255 polymorphism in the *COL3A1* gene is robustly related to Chinese IA incidence. Among other candidate SNPs, rs42524 polymorphism in the *COL1A2* gene is related to IA incidence only in Japanese populations, while high heterogeneity and even contrasting results were observed in other races. In addition, there was a negative association between rs1800238 and IA incidence. For rs2621215, the heterozygous model and the dominant model, but not the allelic model, showed significant associations. However, rs1800238 and rs2621215 were highly influenced by the single study and lack of robustness.

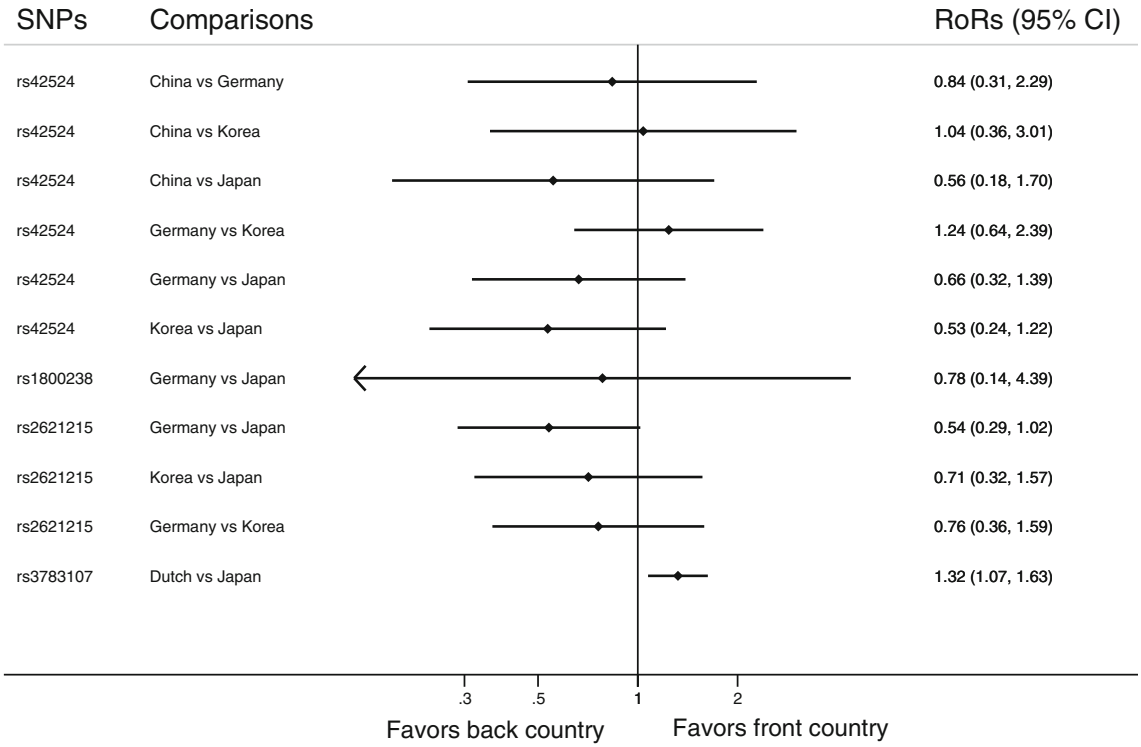


Fig. 3 Forest plot of the prevalence ratio of SNP mutation carriers in different countries. The results showed that for only rs3783107 polymorphism of the COL4A1 gene, the prevalence ratio of mutation carriers in the Dutch population was significantly higher than that in the Japanese population (ROR, 1.31; 95% CI, 1.07–1.63; $p = 0.008$)

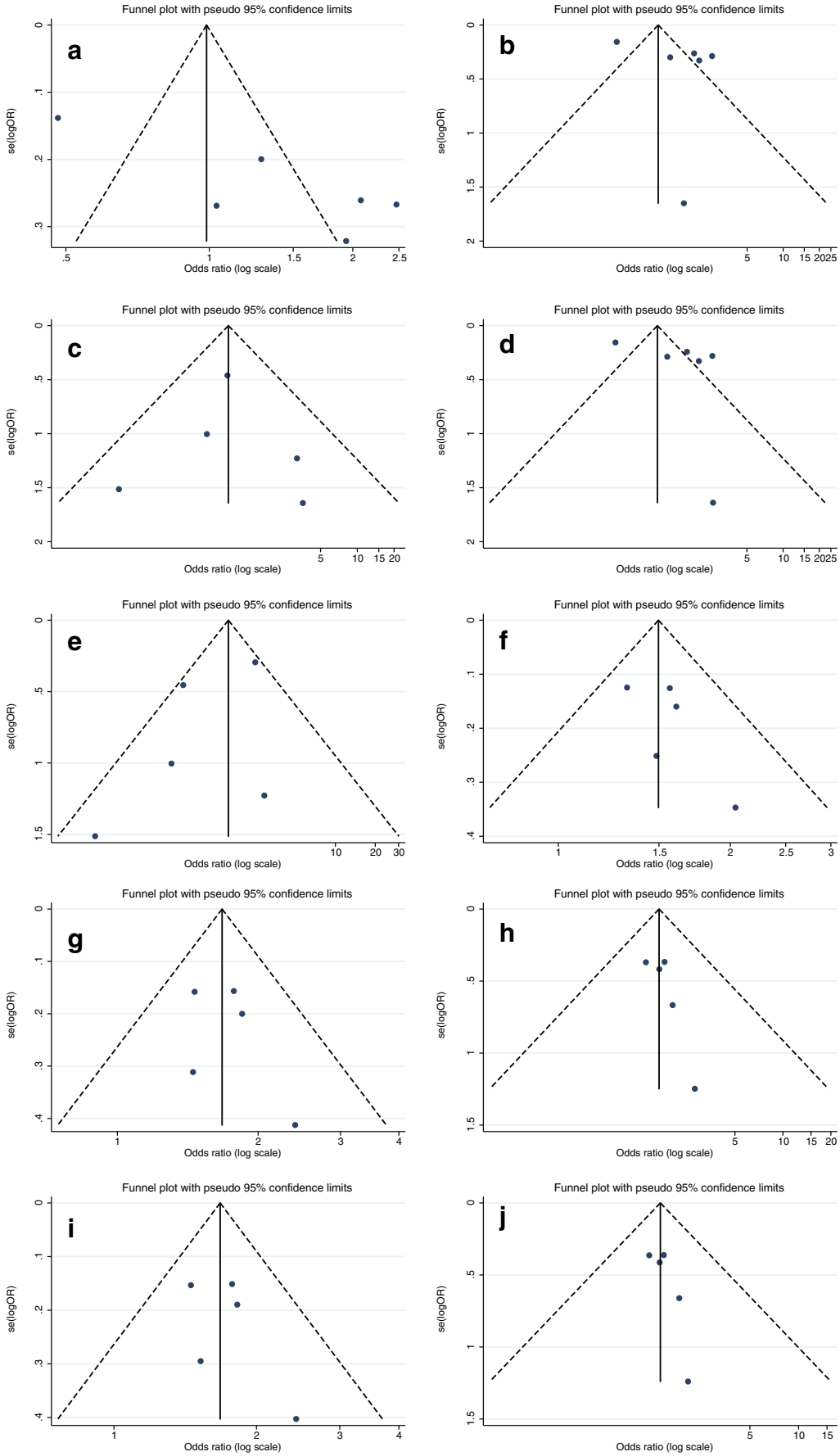
Therefore, the association between the above three SNPs and IA incidence remains controversial. In the *COL4A1* gene, there was a significant association between the rs3783107 polymorphism and IA incidence, and the incidence risk of mutation carriers in the Dutch population was significantly higher than that of the Japanese population. Overall, publication bias did not affect the results (Fig. 4).

The collagen type III is closely related to the elasticity of arterial walls. The rs1800255 polymorphism in *COL3A1* is a benign mutation that causes missense mutations in the *COL3A1* gene at the 698th amino acid from alanine to threonine. This mutation decreases the internal stability and thermal stability of collagen protein [16]. However, another report suggested that the mutation is not sufficient to change vascular structure because of the synergistic action of type III and type I collagen [15]. Based on the results of previous studies, our research indicated that this polymorphism is a genetic risk factor of IA incidence in the Chinese Han population. In addition, the mutation of this locus was also related to Ehler-Danlos syndrome type IV [29], indicating that the mutation would affect the structure of the arterial wall in IA. Therefore, those who carry the mutation should pay close attention to their vascular system to reduce the risk of aneurysm bleeding, such as by avoiding major injury, controlling blood pressure, reducing mood swings, and refraining from smoking, drinking and other unhealthy habits.

Rs42524 in collagen type I was also found to be an important mutation locus in our study, which causes mutation of the 549th amino acid site of *COL1A2* from alanine to proline, thus reducing the thermal stability of the peptide [23]. In addition, this mutation was also correlated with neovascular age-related macular degeneration in the Chinese population [30]. However, the results of our study showed an opposite association between IA incidence and the mutation. Some studies suggested a positive association between the polymorphism and IA [23], whereas others suggested a negative association [17]. The Hardy-Weinberg equilibrium test also revealed a genetic imbalance, and the genetic frequencies are markedly different among different countries [18, 21, 25]. Therefore, whether there is an association between rs42524 and IA incidence requires further research.

The rs1800238 polymorphism showed a negative association with IA incidence. However, the change of this locus did not cause the amino acid change. However, previous studies found that it may be associated with Ehlers-Danlos syndrome,

Fig. 4 Funnel plots to test for publication bias. Funnel plots were generated if the number of included studies was greater than four. Publication bias was found in the allelic model of rs42524 (**a**) but not in the heterozygous model (**b**), homozygous model (**c**), dominant model (**d**), and recessive model (**e**). There was no publication bias in the allelic model (**f**), heterozygous model (**g**), homozygous model (**h**), dominant model (**i**), and recessive model (**j**) of rs1800255 ▶


Funnel plot with pseudo 95% confidence limits
a
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
b
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
c
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
d
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
e
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
f
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
g
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
h
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
i
se(logOR)
Odds ratio (log scale)
Funnel plot with pseudo 95% confidence limits
j
se(logOR)
Odds ratio (log scale)

dermatosparaxis type [31], and impaired osteogenesis [32]. Rs2621215 is located in the *COL1A2* gene at intron 46, and its polymorphism does not change the amino acid sequence. Its mutation in Japanese subjects was found to be associated with IA onset, but not in Korean and German populations. Rs3783107 is also located in the intron region of *COL4A1* and does not affect the amino acid sequence. There was association between rs3783107 and IA only in the Dutch population. Although the above two loci do not directly affect the amino acid sequences, it may affect non-coding ribose nucleic acid (RNA) transcription and the regulation of other protein expression that cause disease occurrence.

It was difficult for us to identify the genes responsible for IA because IA onset is caused by combined effects, including polygenic inheritance, hemodynamic effects, and acquired degeneration. In addition, other undetected SNPs associated with IA pathogenesis still need to be studied. In addition to the related genes that have been researched, including *collagen*, *ACE*, *elastin*, *eNOS*, *IL-6*, etc., microRNA has also been found to be related to IA incidence. In addition, case-control studies and genome-wide studies continue to identify potential disease-related SNPs. It is also possible to consider SNPs as risk factors, which has been confirmed in previous studies, to determine their association with IA and to predict IA incidence via logistic regression analyses.

Several limitations exist regarding our study. Our study was performed at the study level, but not at the individual level. Some SNP results were affected only in a single previous study, such as rs1800238 and rs2621215. In addition, the low number of included studies likely affected the accuracy of the results. Finally, as a polygenic inheritance disease, more studies are needed to confirm the effects of the related genes on the pathogenesis of IA.

Conclusion

In this meta-analysis, we systematically analyzed SNPs from four collagen-related genes, which indicated that rs1800255 polymorphism in the *COL3A1* gene is robustly correlated with IA in the Chinese population. The rs42524 polymorphism in the *COL1A2* gene was correlated with IA only in Japanese, but not in other populations. In addition, rs1800238 in *COL1A2* was negatively correlated with IA and rs2621215 in the *COL1A2* gene was associated with IA only in the heterozygous model and the dominant model, although both associations lacked robustness. The rs3783107 mutation in *COL4A1* was significantly associated with IA in the Dutch population, and the risk of mutation carriers in the Dutch population was significantly higher than that in the Japanese population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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