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Original Article

Genetic polymorphisms and the susceptibility to brain arteriovenous malformation

Xiang Gao[1], Tiefeng Zhang[1,2], Zhepei Wang[1], Jikuang Zhao[1], Sheng Nie[1], Jie Sun[1], Keqing Li[1], Shiwei Duan[2], Yi Huang[1]

[1]*Department of Neurosurgery, Ningbo First Hospital, Ningbo, Zhejiang, China;* [2]*Zhejiang Provincial Key Laboratory of Pathophysiology, School of Medicine, Ningbo University, Ningbo, Zhejiang, China*

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Abstract: Brain arteriovenous malformation (BAVM) is the most cause of intracranial hemorrhage (ICH) in young adults. The aim of this study is to investigate the contribution of genetic polymorphisms to the risk of BAVM. We performed a systematic overview of genetic studies for the susceptibility of BAVM from PubMed, Google, and China National Knowledge Infrastructure (CNKI). We screened all the available studies to harvest the eligible SNPs that were involved in at least two independent datasets. Our comprehensive literature search identified nine polymorphisms that were eligible for the current meta-analysis. Among the nine SNPs, we found significant associations with increased BAVM risk for *CDKN2B-AS1* rs1333040 (odds ratios (OR) = 1.24, 95% confidence intervals (CI) = 1.07-1.43, P = 0.003) and *ALK1* rs2071219 (OR = 1.86, 95% CI = 1.32-2.62, P < 0.001). Strong connections with ICH risk in BAVM patients were showed in the *IL6* rs1800795 (additive model: OR = 2.02, 95% CI = 1.34-3.07, P = 0.001, I^2 = 2.5%; dominant model: OR = 2.22, 95% CI = 1.34-3.68, P = 0.002) and *TNFα* rs361525 (additive model: OR = 2.26, 95% CI = 1.35-3.78, P = 0.002, I^2 = 18.8%; dominant model: OR = 2.35, 95% CI = 1.35-4.07, P = 0.002). In conclusions, our results suggested that the *CDKN2BAS1* rs1333040 and *ALK1* rs2071219 were significantly associated with BAVM risk. *IL6* rs1800795 and *TNFα* rs361525 were strongly correlated with the ICH risk in BAVM patients.

Keywords: Brain arteriovenous malformation, single nucleotide polymorphism, intracranial hemorrhage, genetic, meta-analysis

Introduction

Brain arteriovenous malformation (BAVM) is a type of cerebrovascular disease which is characterized by excessive angiogenesis and vascular remodeling [1, 2]. Although technical advances have changed the treatment of BAVM dramatically in the last years, the outcome of patients still has a poor prognosis [3]. BAVM is the most cause of intracranial hemorrhage (ICH) in young adults [4]. It is still a challenge to predict the risk of the BAVM and BAVM-ICH in neurosurgery [5, 6]. Recently, researchers have confirmed that this disease is significantly associated with the interaction of genetics and environment [7, 8]. Accumulating evidences have reported that genetic variations are susceptibility to BAVM [9]. Linkage studies in different BAVM families also found many loci, including three well established regions (5p13-q14, 15q11-q13, and 18p11) [10] and seven candidate regions (3q27, 4q34, 6q25, 7p21, 13q32-33, 16p12-13, and 20q11-13) [11]. Candidate genetic studies have identified BAVM related single nucleotide polymorphisms (SNPs) in *CDKN2B-AS1* [12], G protein-coupled receptor 124 (*GPR124*) [13], matrix metalloproteinase 9 (*MMP-9*) [14], and Angiopoietin-like 4 (*ANGPTL4*) [15]. The roles of genetic mechanisms in BAVM development were confirmed by several mouse model studies [16, 17].

Recent, study has confirmed that SNPs located in the pathways involving inflammatory and angiogenic signals showed significant association with the risk of sporadic BAVM [18]. There are multiple variants potentially influence their pathogenesis and clinical course in BAVMs. Such as, the variation of matrix metallo proteinase 3 (*MMP3*) promoter affects transcription

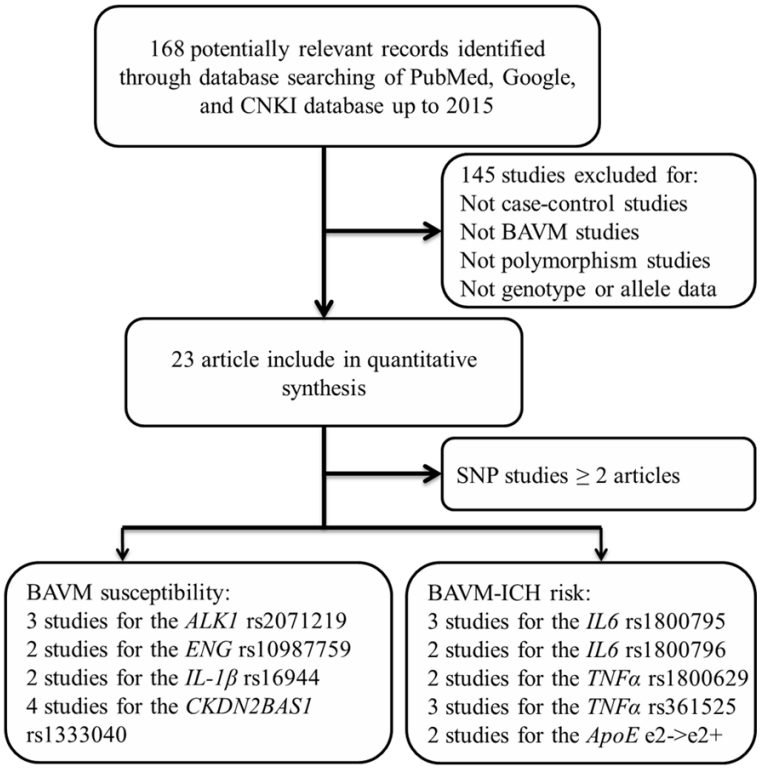

Figure 1. Flow diagram of the stepwise selection from relevant studies.

activity in BAVM [19]. *MMP9* polymorphism rs9509 may be associated with ICH in patients with BAVM [14]. And functional polymorphisms within the interleukin-1 (*IL1*) cluster gene are associated with BAVMs and influence the clinical characteristics [20].

Over the past decade, many studies were conducted to evaluate the association between SNPs and the risk of BAVM or BAVM-ICH. However, the results are inconsistent in various variants locus. In the current study, we perform a comprehensive meta-analysis to evaluate the effect of SNPs on BAVM risk.

Methods and materials

Publication search

Candidate studies for the current meta-analyses were retrieved after a search from 2004 to 2015 in the electronic databases including PubMed, Google, and China National Knowledge Infrastructure (CNKI). The keywords included "brain arteriovenous malformation(s)" or "cerebral arteriovenous malformation(s)" or "intracranial arteriovenous malformation(s)", together with "polymorphism(s)" or "allele" or "genotype" or "variant". Full text articles were read to select the interested information. References listed on the retrieved articles and previous meta-analyses on this subject were searched to appraise other studies of potential relevance.

Inclusion criteria

Studies were included in our meta-analysis if they were case-control or cohort studies and provided available genotype or allele frequencies in both cases and controls, or have sufficient data to infer the odds ratios (ORs) and 95% confidence intervals (CIs). In addition, the genotype distribution in controls should meet Hardy-Weinberg equilibrium (HWE).

Data extraction

All data were independently extracted from the studies by two of the authors in the meta-analysis as followed: first author's name, year of publication, study design, ethnicity, the number of cases and controls, country of the study.

Statistical analyses

Genotype distribution in case and control groups was tested for departure from HWE using Arlequin program (version 3.5). Power analysis was performed using the Power and Sample Size Calculation software (version 3.0.43). The OR and 95% CI were calculated to evaluate the association between polymorphisms and BAVM risk. The meta-analyses were performed using the Stata software (version 11.0, Stata Corporation, College Station, TX) [21]. A chi-square-based Q statistic test was calculated for the heterogeneity of studies in the meta-analysis. The inconsistency index (I^2 statistic) was also examined, and a value of $I^2 > 50$ indicated the existence of heterogeneity. The pooled OR was estimated with models based on fixed effect or random effect model.

Table 1. Main characteristics of studies included in the meta-analysis of BAVM

SNP/Author (year)	Ethnic	Case/Control (n)	Genotype (n)			Allele (n)	
ALK1 rs2071219			AA	AG	GG	A	G
Simon M (2006)	German	101/202	42/57	48/100	11/45	132/214	70/190
Pawlikowska L (2005)	American	170/129	56/37	91/56	23/36	203/130	137/128
Kim B(2014)	Dutch	139/353	44/123	73/161	22/69	161/407	117/299
ENG rs10987759			AA	AG	GG	A	G
Pawlikowska L (2005)	American	169/128	147/102	22/25	0/1	316/229	22/27
Kim B (2014)	Dutch	140/355	120/301	20/50	0/4	260/652	20/58
IL-1β rs16944		CC	CC	CT	TT	C	T
Kim H (2008)	American	231/255	89/110	102/128	40/17	280/348	182/162
Fontanella M (2012)	Italian	101/210	39/84	51/99	11/27	129/267	73/153
CKDN2B-AS1 rs1333040		TT	TT	TC	CC	T	C
Sturiale CL (2013)	Rome, Italian	78/103	43/36	28/52	/7/15	114/124	42/82
Sturiale CL (2014)	Turin, Italian	106/171	46/103	54/66	/6/2	146/272	66/70
Kremer P (2014)	Dutch	160/1036	NA	NA	NA	170/1140	150/932
Bendjilali N (2014)	American	338/510	NA	NA	NA	419/579	257/441

Table 2. Main characteristics of studies included in the meta-analysis of ICH

SNP/Author (year)	Ethnic Group	Case/Control (n)	Genotype (n)		Allele (n)	
IL6 rs1800795			GG	GC+CC	G	C
Pawlikowska L (2004)	American	69/103	48/48	21/55	NA	NA
Chen Y (2006)	American	16/25	13/11	3/14	28/34	4/16
Achrol AS (2006)	American	17/251	10/148	7/103	NA	NA
IL6 rs1800796			GG	GC+CC	G	C
Pawlikowska L (2004)	American	71/104	46/74	25/30	NA	NA
Achrol AS (2006)	American	17/259	11/187	6/72	NA	NA
TNFα rs1800629			GG	GA+AA	G	A
Pawlikowska L (2004)	American	69/104	60/78	9/26	129/182	9/26
Achrol AS (2006)	American	18/254	14/199	4/55	32/453	4/55
TNFα rs361525			GG	GA+AA	G	A
Pawlikowska L (2004)	American	70/104	60/92	10/12	130/196	10/12
Achrol AS (2006)	American	18/262	12/236	6/26	30/498	6/26
Achrol AS (2007)	American	34/176	26/158	8/18	60/334	8/18
ApoE e2- > e2+			e2-	e2+		
Pawlikowska L (2006)	American	18/266	14/234	4/32	NA	NA
Achrol AS (2007)	American	33/179	28/158	5/21	NA	NA

Meta-analysis with significant heterogeneity (I^2 > 50%) was performed using the random effect model; otherwise, a fixed effect model would be applied. Z test was used to conclude the pooled OR and a $P < 0.05$ was considered to be statistically significant.

Results

Study characteristics

The details of the literature search were given in the flow diagram of **Figure 1**. Our initial search for the genetic studies of BAVM retrieved 168 articles from PubMed, Google, and CNKI from 2004 to 2015. After screening from the medical literature, four SNPs (*ALK1* rs20712-19, *ENG* rs10987759, *IL-1β* rs16944, and *CDKN2B-AS1* rs1333040) were studied in more than one manuscript for their associations with BAVM susceptibility, and five SNPs (*IL6* rs1800796, *IL6* rs1800795, *TNFα* rs18-00629, *TNFα* rs361525 and *APOE* e2+/e2-) for their associations with the risk of BAVM with ICH. Therefore, these polymorphisms were enrolled in the meta-analyses. The genotype

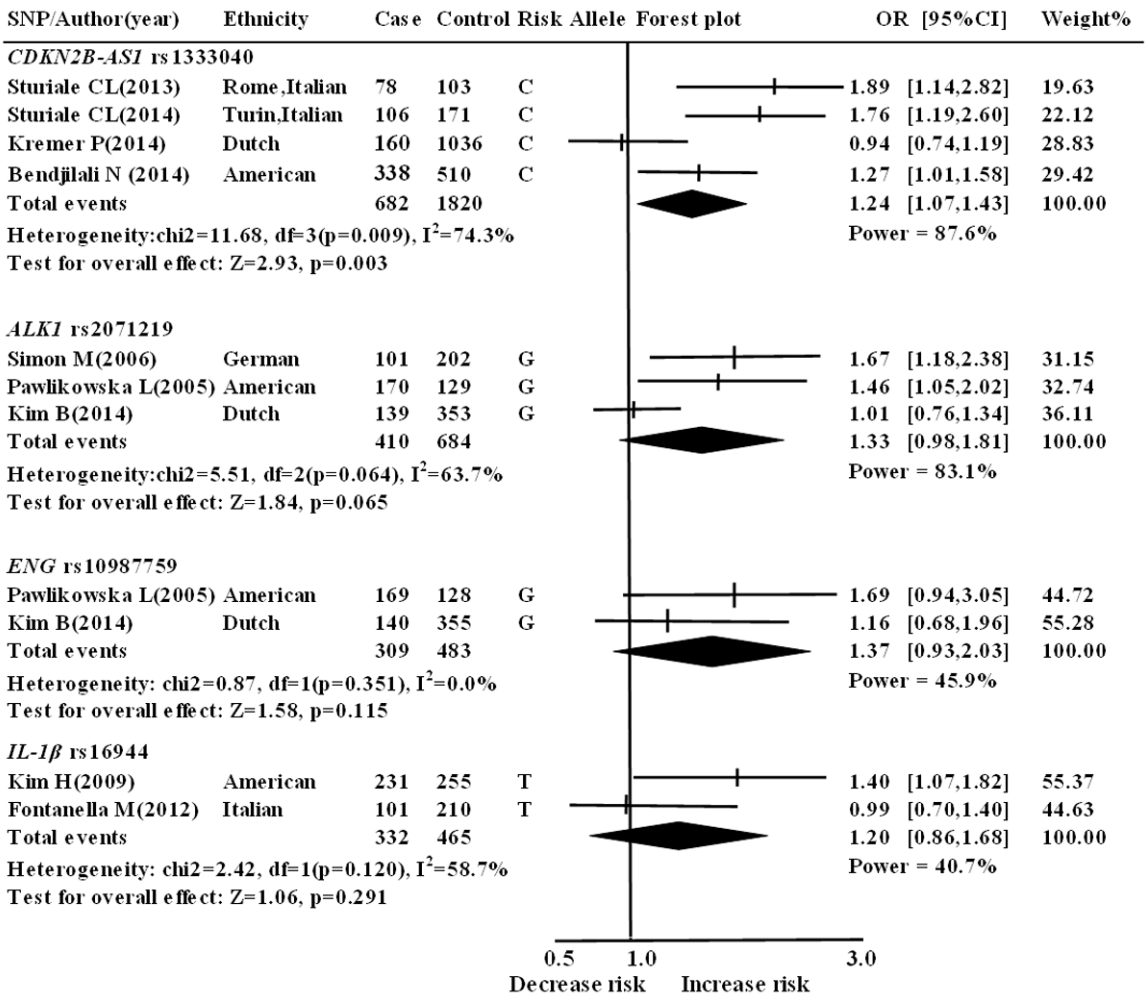

Figure 2. Forest plots for four polymorphisms and BAVM under allele model.

and allele frequencies of the four SNPs in both BAVM and control groups were listed in **Table 1**. There were three studies on the *ALK1* rs2071219 [22-24], two studies on the *ENG* rs10987759 [23, 24] and *IL-1β* rs16944 [20, 25], four articles on the *CDKN2B-AS1* rs1333040 [9, 12, 26, 27]. The genotype distributions of the enrolled SNPs between ICH and No-ICH BAVM patients were shown in **Table 2**. There were three studies on the *IL6* rs1800795 [28-30] and *TNFα* rs361525 [28, 30, 31], two studies on the *IL6* rs1800796 [28, 30], *TNFα* rs1800629 [28, 30], and *APOE* e2+/e2- [31, 32].

Meta-analysis of the association between SNPs and the risk of BAVM under various genetic models

As shown in **Figure 2**, the meta-analysis of *CDKN2B-AS1* rs1333040 included 682 BAVM patients and 1820 healthy controls among four studies in the additive model. The result indicated a significant association of the *CDKN2B-AS1* rs1333040 with BAVM risk (OR = 1.24, 95% CI = 1.07-1.43, P = 0.003, Power = 87.6%) and a strong heterogeneity in the meta-analysis (I^2 = 72.2%, P = 0.013).

The main results of the meta-analysis of four SNPs with BAVM risk were shown in **Table 3**. The meta-analysis of *ALK1* rs2071219 included 410 BAVM patients and 684 healthy controls among three studies. Significant association was observed in *ALK1* rs2071219 under the dominant model (OR = 1.86, 95% CI = 1.32-2.62, P < 0.001, I^2 = 36.7%, Power = 99.3%). However, no association of *ALK1* rs2071219 with BAVM were found under the additive model (OR = 1.33, 95% CI = 0.98-1.81, P = 0.065) and recessive model (OR = 1.19; 95% CI = 0.78-1.82, P = 0.423).

Table 3. Meta-analysis of SNPs in three genetic models#

Gene	SNP	Case/ Control	Additive model			Dominant model			Recessive model		
			OR [95% CI]	P(z)	I^2 (%)	OR [95% CI]	P(z)	I^2 (%)	OR [95% CI]	P(z)	I^2 (%)
CDKN2B-AS1	rs1333040	682/1822	1.24 [1.07, 1.43]a	0.003	72.2	NA	NA	NA	NA	NA	NA
ALK1	rs2071219	410/684	1.33 [0.98, 1.81]a	0.065	63.7	1.86 [1.32, 2.62]b	< 0.001	36.7	1.19 [0.78, 1.82]a	0.423	58.9
ENG	rs10987759	309/483	1.37 [0.93, 2.03]b	0.115	0.0	NA	NA	NA	NA	NA	NA
IL-1β	rs16944	332/465	1.20 [0.86, 1.68]a	0.291	58.7	1.58 [0.46, 5,51]a	0.471	85.3	1.15 [0.86,1.54]b	0.336	0.0
IL6	rs1800795	102/379	2.02 [1.34-3.07]b	0.001	2.5	2.22 [1.34-3.68]a	0.002	52.8	NA	NA	NA
IL6	rs1800796	88/363	NA	NA	NA	1.36 [0.79-2.36]b	0.270	0.0	NA	NA	NA
TNFα	rs1800629	87/358	1.58 [0.83-2.98]b	0.161	16.9	1.67 [0.85,3.27]b	0.134	24.4	NA	NA	NA
TNFα	rs361525	122/542	2.26 [1.35-3.78]b	0.002	18.8	2.35 [1.35-4.07]b	0.002	39.8	NA	NA	NA
ApoE	e2- > e2+	51/445	NA	NA	NA	1.64 [0.75-3.58]b	0.218	0	NA	NA	NA

#: The power of *CDKN2B-AS1* rs1333040 in the additive model is 87.6%. The power of *ALK1* rs2071219 in the dominant model is 99.3%. The power of *IL6* rs1800795 in the dominant model is 90.3%. The power of *TNFα* rs361525 in the dominant model is 87.5%. NA: not analyzed. a: random effected model; b: fixed-effected model.

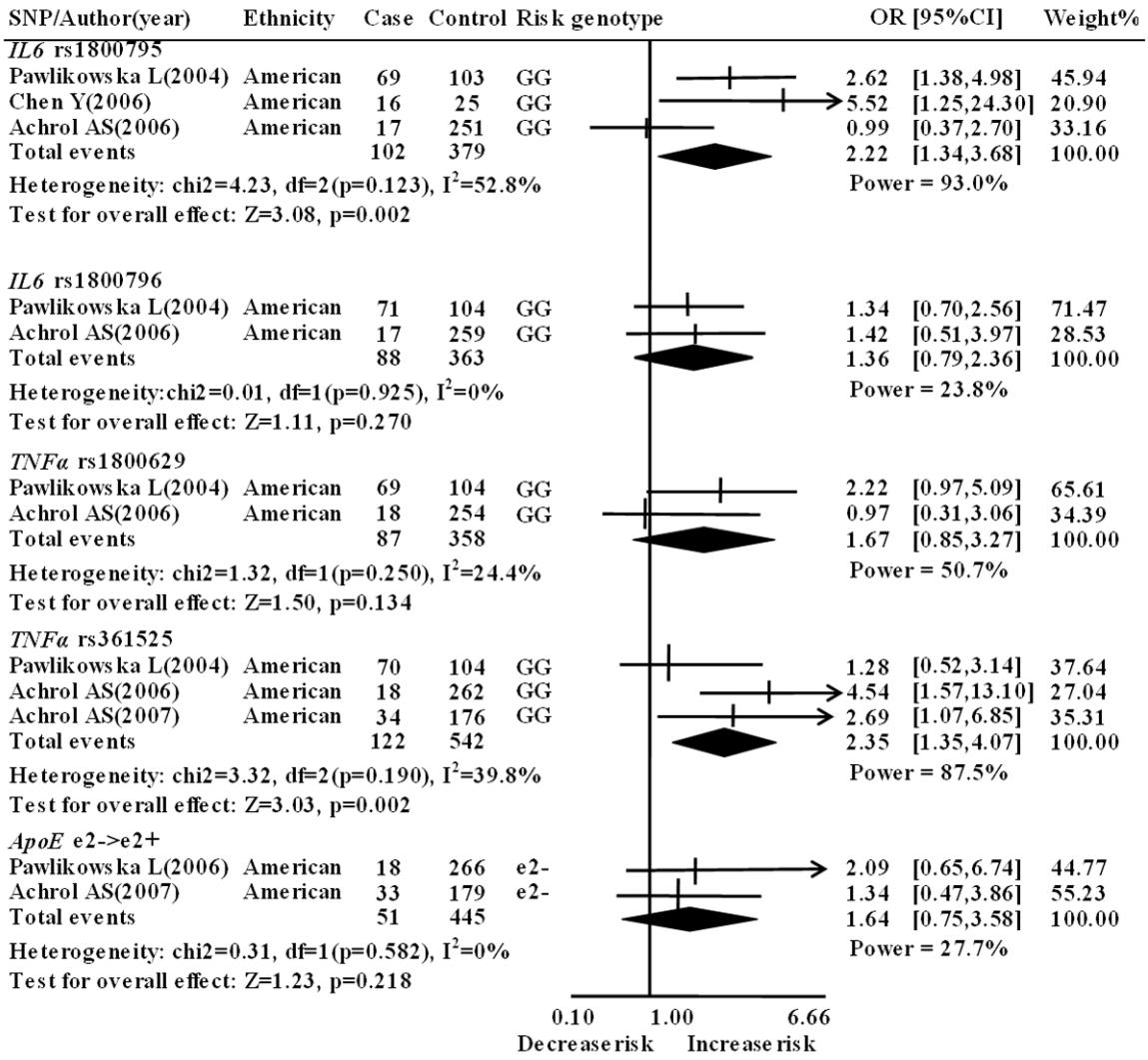

Figure 3. Forest plots for five polymorphisms and BAVM-ICH patients.

The meta-analysis of *ENG* rs10987759 included 309 BAVM patients and 483 healthy individuals among two studies (**Table 3**). Our results could not find any connection between *ENG*

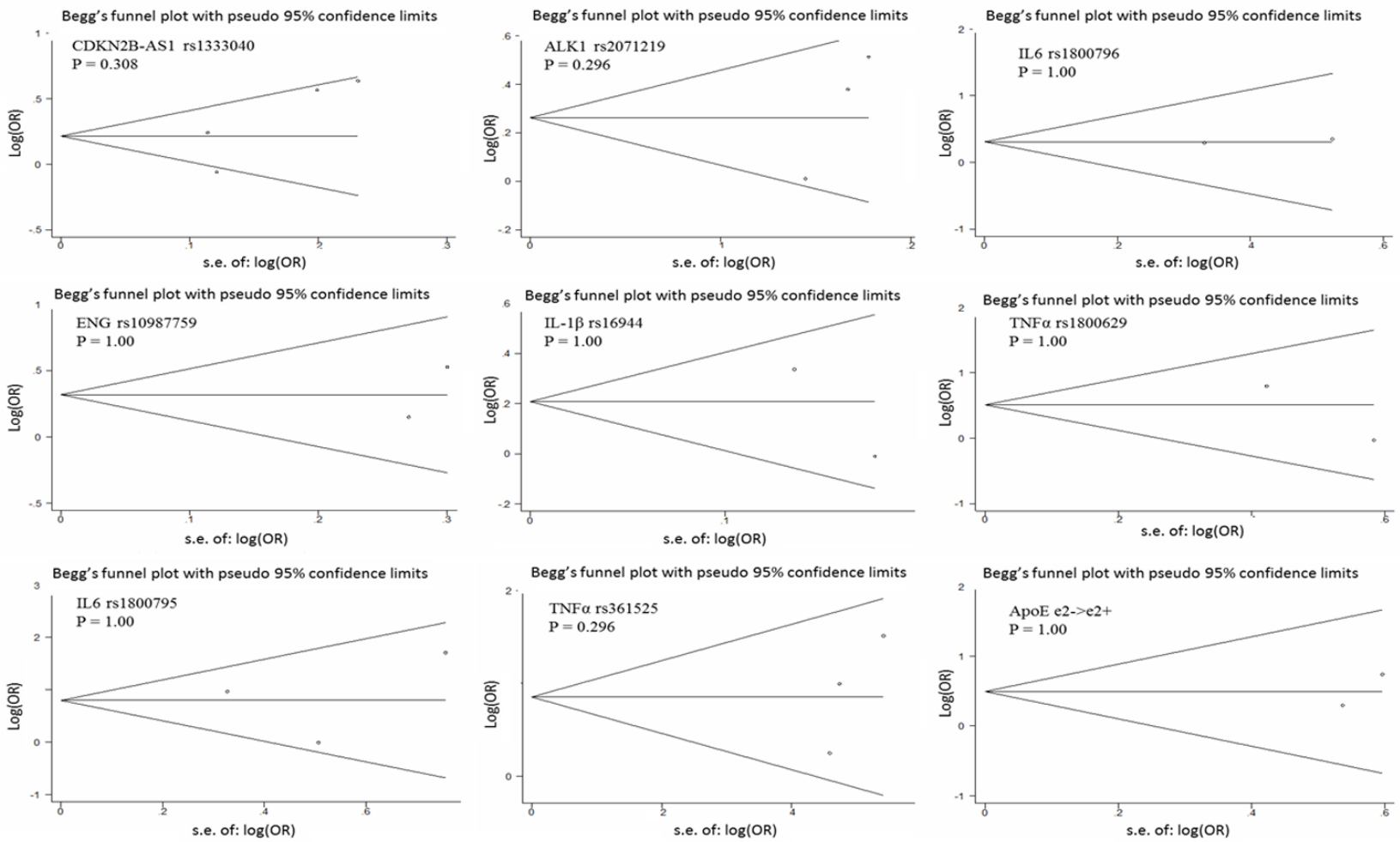

Figure 4. Publication bias analysis for the SNPs in the meta-analysis.

rs16930129 and BAVM risk (OR = 1.37; 95% CI = 0.93-2.03, P = 0.115). There was no evidence of statistical heterogeneity in the meta-analysis of *ENG* rs16930129. There were 332 patients and 465 controls collected for the meta-analysis of *IL-1β* rs16944. However, no association was found between rs16944 and BAVM in the three genetic models (additive: OR = 1.20, 95% CI = 0.86-1.68, P = 0.291; dominant: OR = 1.58, 95% CI = 0.46-5.51, P = 0.471; recessive: OR = 1.15, 95% CI = 0.86-1.54, P = 0.336).

Meta-analysis of the association between SNPs and the risk of BAVM-ICH

The main results of the meta-analysis of five SNPs with BAVM-ICH risk were shown in **Table 3**. The forest plot for the five SNPs was shown in **Figure 3**. Meta-analysis of *IL6* rs1800795 was involved with 3 case-control studies among 379 controls and 102 cases. Our results showed that *IL6* rs1800795 was significantly associated with ICH risk in the BAVM patients (additive model: OR = 2.02, 95% CI = 1.34-3.07, P = 0.001, I^2 = 2.5%; dominant model: OR = 2.22, 95% CI = 1.34-3.68, P = 0.002, I^2 = 52.8%, Power = 93.0%). Meta-analysis of *TNFα* rs361525 with 3 case-control studies among 544 controls and 122 cases revealed a strong relationship with ICH risk in BAVM patients (additive model: OR = 2.26, 95% CI = 1.35-3.78, P = 0.002, I^2 = 18.8%; dominant model: OR = 2.35, 95% CI = 1.35-4.07, P = 0.002, I^2 = 39.8%, Power = 87.5%). No evidence of statistical association was observed for three SNPs (P > 0.05).

Publication bias

Publication bias was analyzed by Begg's test. No publication bias of all the nine tested SNPs was found using the Begg's funnel plot (**Figure 4**, Begg's corrected value *P* > 0.1).

Discussion

BAVM is a complex disease caused by vascular anomalies. Genetic factors may play an important role in the formation of disease. A comprehensive analysis of the genetic mechanism underlying BAVM development is of crucial importance for management policy. In this study, we performed a systematic overview of genetic studies for the susceptibility of BAVM. We screened all the available studies to harvest the eligible SNPs that were involved in at least two independent datasets. Our results showed that *CDKN2BAS1* rs1333040 (P = 0.006 in the additive model) and *ALK1* rs2071219 (P < 0.001 in the dominant model) were significantly associated with BAVM risk. *IL6* rs1800795 (OR = 2.22, P = 0.002) and *TNFα* rs361525 (dominant model: OR = 2.35, P = 0.002) were strongly correlated with the ICH risk in BAVM patients.

Activing-like kinase 1 (ALK1) was a receptor in the TGF beta signaling pathway. *ALK1* mutations were associated with hemorrhagic telangiectasia type 2 [33], pulmonary arteriovenous malformations [34] and sporadic BAVM [23]. The polymorphism rs2071219 was located in the intronic region of *ALK1* on chromosome 12q13.13, which might play a role in the transcription regulation. Previous studies showed that rs2071219 was significantly associated with BAVM susceptibility [22, 23]. Pawlikowska et al' s study [23] proved that rs2071219 had a 247% increase risk factor for BAVM in the American mixed population under the dormant model (AA+AG vs GG). Simon et al's study [22] reported that the rs2071219-G allele was significantly more frequent among arteriovenous dysplasia patients compared with controls in Germany. However, Boshuisen et al's study [24] could not find any association between *ALK1* polymorphisms and BAVM risk in 503 Dutch volunteers. The above discrepancy might be due to lack of power in the research. Our meta-analysis collected 410 BAVM patients and 684 healthy controls showed that *ALK1* rs2071219 was a significant risk factor of BAVM in the dominant model with a power of 99.3%.

CDKN2BAS1 gene locates on chromosome 9p21, which was a large antisense non-coding RNA and differentially expressed in vascular endothelial cells and smooth coronary muscle cells [35]. Common variants on 9p21 were more strongly associated with both intracranial and extracranial vascular diseases [36, 37]. SNP rs1333040 on chromosome 9p21.3 was located in *CDKN2BAS1*. This polymorphism had been proved to be a susceptible locus of BAVM risk in Italians [26] and Americans [9]. However, the significant association could not be found in 160 Dutch BAVM patients [27]. Our analysis enrolled more than 2000 individuals

testified that *CDKN2BAS1* rs1333040 was a significant risk factor of BAVM.

Inflammation played an important role in the pathogenesis of several vascular malformations including intracranial aneurysms [38], cerebral cavernous malformations [39], and BAVM [40, 41]. Interleukin 6 (IL-6) was an interleukin that acted as both pro-inflammatory [42] and anti-inflammatory cytokine [43]. It was an important mediator of the acute phase of the inflammatory response. *IL-6* gene variants might play a key role in dysplasia and rupture of intracranial vessels [44]. The genotype rs1800795-GG of the *IL6* gene showed a 262% increases risk of hemorrhagic presentation in BAVM patients [28]. The significant association was further strengthened by our meta-analysis. Our study among 481 patients confirmed a 222% increased risk of bleeding in subjects carrying the GG genotype.

Tumor necrosis factor alpha (TNFα) was also a pro-inflammatory cytokine that had crucial immunomodulatory properties and proteolytic processes [45]. *TNFα* rs361525 was shown to have a 4-fold increased risk of bleeding in BAVM patients [30]. Our study collected three studies among more than 660 patients, and suggested a significantly increased risk factor of hemorrhagic presentation in patients with BAVM (OR = 2.35, 95% CI = 1.35-4.07, P = 0.002).

Finally, several limitations in our meta-analyses should be taken into consideration. Screening all the medical literatures, there were only nine SNPs were studied in more than one study for their association with BAVM. The samples were only limited in the enrolled studies. The results of this work might not stand for all ethnic populations. Future investigations with large samples in other populations might help clarify the contribution of the SNPs of interest to BAVM.

In conclusion, our study showed that *CDKN2BAS1* rs1333040 and *ALK1* rs2071219 were significantly associated with BAVM risk. *IL6* rs1800795 and *TNFα* rs361525 were strongly correlated with the ICH risk in BAVM patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yi Huang, Department of Neurosurgery, Ningbo First Hospital, Ningbo 315010, Zhejiang, China. Tel: 86-574-87085517; Fax: 86-574-87085517; E-mail: huangy102@gmail.com

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