

Genetic associations of intracranial aneurysm formation and sub-arachnoid hemorrhage

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ABSTRACT

Risk factors for cerebral aneurysms typically include age, hypertension, smoking, and alcohol usage. However, the possible connection of aneurysms with genetic conditions such as Marfan's syndrome, polycystic kidney disease, and neurofibromatosis raises the question of possible genetic risk factors for aneurysm, and additionally, genetic risk factors for rupture. We conducted a literature review using the PubMed database for studies regarding genetic correlation with cerebral aneurysm formation as well as rupture from December 2008 to Jun 2015. Twenty-one studies related to IA formation and 10 concerning IA rupture that met our criteria were found and tabulated. The most studied gene and the strongest association was 9p21/CDKN2, which is involved in vessel wall remodelling. Other possible genes that may contribute to IA formation include EDNRA and SOX17; however, these factors were not studied as robustly as CDKN2. Multiple factors contribute to aneurysm formation and rupture and the contributions of blood flow dynamics and comorbidities as mentioned previously, cannot be ignored. While these elements are important to development and rupture of aneurysms, genetic influence may predispose certain patients to formation of aneurysms and eventual rupture.

Key words: Formation, genetics, intracranial aneurysm, rupture, sub-arachnoid hemorrhage

Introduction

The prevalence of unruptured intracranial aneurysms (IAs) in the general population is estimated to be approximately 3%.^[1] Traditional risk factors for unruptured aneurysms include female gender and older age, hypertension, the diameter of the aneurysm, alcohol use, and tobacco use.^[2,3] The most worrisome event in patients harboring an IA is the rupture of the arterial wall and resultant sub-arachnoid hemorrhage (SAH), which occurs at a rate of 30,000 per year in the United States^[4] and carries a mortality rate of up to 45%.^[2-5] Given the fact that IA can remain asymptomatic until the time of rupture and that approximately 80–90% of unruptured aneurysms discovered

incidentally, it is critical to better understand the variables that may be associated with higher chances of aneurysm formation, growth, and rupture.^[2]

Multiple genetic diseases have been identified as having a possible association with IA. Marfan's syndrome involves defects in the gene FBN1 (which codes the extracellular matrix protein fibrillin-1) and is classically associated with aortic dissection, possibly due to structural compromise of arterial cells caused by the mutation.^[5,6] Although an association between Marfan's syndrome and IA has also been suggested,^[5-7] autopsy studies and analysis of a family multiple members suffering from IA and Marfan's syndrome have not always shown an association.^[5,8] Neurofibromatosis type I (NF1) is caused by a mutation that affects the neurofibromin gene on chromosome 17q, which not only is tumor suppressor but may

Access this article online	
Quick Response Code:	Website: www.asianjns.org
	DOI: 10.4103/1793-5482.180972

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How to cite this article: Theodotou CB, Snelling BM, Sur S, Haussen DC, Peterson EC, Elhammady MS. Genetic associations of intracranial aneurysm formation and sub-arachnoid hemorrhage. Asian J Neurosurg 2017;12:374-81.

also exert some effect on tubulin as well.^[9] NF1 manifestations include café-au-lait spots, neurofibromas, and gliomas. The association of NF1 with IA has also been suggested, albeit with mixed evidence.^[9,10] Autosomal dominant polycystic kidney disease (ADPKD) is an inherited renal condition which is caused by mutations in two known genes: PKD1 (85–90% of cases) and PKD2 (10–15% of cases). The mutation results in the formation of multiple renal cysts and eventually renal failure. Patients with ADPKD may have an increased risk of IA formation with prevalence rates estimated to be between 3% and 12%.^[11,12] It is believed that the affected genes produce flawed polycystin that leads to structural weaknesses in vascular smooth muscle cells.^[13] Based on these genetic diseases, there appears to be a connection between certain genetic traits and IA, which may be indicative of a common element in their formation.

In addition to the aforementioned genetic disorders, there are less obvious variations in the genetic code, which may also play a role in the development and rupture of cerebral aneurysms. Increased familial risk indicates a possible genetic risk.^[14–16] Specific variations in the genetic code (polymorphisms) and certain loci have also been implicated as having a genetic influence on IA formation.^[17,18] A better understanding of the genetic influence on aneurysm formation and rupture risk may aid clinicians in the identification of patients at higher risk for SAH. We sought to review the current literature regarding the genetic factors associated with aneurysm formation and rupture.

Materials and Methods

Our study was divided into two sections: Genetic factors related to IA formation and IA rupture. We performed literature searches using the PubMed database to find relevant literature on these topics. Formal searches were conducted using MeSH database advanced search tool with the MeSH phrases “IA” and “genetics,” “IA” and “gene,” “SAH/genetics” and “(IA) and (rupture) and (genetics).” We limited the inclusion to only articles containing human subjects, available in English, and conducted within 6.5 years (December 2008–June 2015).

Articles were excluded if they did not meet any of the aforementioned criteria or were a case report, single-family study, meta-analysis, or were an analysis of inter-genetic relationships rather than relationship with IA formation or rupture. Studies were also excluded if they concerned non IA or included non IA in their analysis.

We recorded the number of patients and controls and the polymorphisms from each study. For each polymorphism, the location of the polymorphism (and associated gene if known), the odds ratio (OR) (and 95% confidence interval [% CI], if available), and the *P* value were recorded. In cases where a study sampled multiple geographically different populations, the combined results of the populations found in that particular study were collected.

Results

Twenty-one studies related to IA formation and 10 concerning IA rupture that met our criteria were found and are listed in Tables 1 and 2, respectively.

Aneurysm Formation

The total number of IA patients from these studies was 19,997 while total number of controls was 51,953. Thirty-two different genetic locations were investigated for possible association with IA, as shown in Table 1.

Three genes were consistently shown to have associations with IA formation: CDKN2 (6 studies), EDNRN, (2) and SOX17 (2). Among these genes, only CDKN2 had polymorphisms (rs10757272, rs1333040, rs2891168) found to be associated with IA by multiple studies. Polymorphisms from EDNRN and SOX17, although associated with IA formation, were different between studies.

Of these three genes, the one which showed the most robust association with IA was CDKN2, a gene associated with cyclin-dependent kinase (CDK) inhibitors, polymorphism rs1333040 (OR = 1.43, 95% CI = 1.24–1.66, *P* < 0.001). However, this same polymorphism was examined in two other studies in our sample and yielded less dramatic although still significant results (OR = 1.31, 95% CI = 1.25–1.39, *P* < 0.001; OR = 1.28, 95% CI = 1.04–1.57, *P* = 0.02).^[50,51] There were a total of eleven distinct CDKN2 polymorphisms in the sample, all of which showed significant association with IA. The association between CDKN2 rs1333040 and IA was the strongest found in our entire sample. Among the other genes with repeated association with IA, the strongest association of SOX17, a regulator of growth and maintenance of the vascular endothelium, came from rs9298506 (OR = 1.28, 95% CI = 1.20–1.38, *P* < 0.001) while the most robust association from EDNRN, a gene associated with the Endothelin-1 receptor that controls vascular smooth muscle tone, came from polymorphism rs6842241 (OR = 1.25, 95% CI = 1.16–1.34, *P* < 0.001).^[39,50,52] In our sample, two distinct polymorphisms each for both SOX17 and EDNRN were analyzed and showed significant association with IA. The range of OR for CDKN2 was 1.21–1.43, the range for EDNRN was 1.22–1.25, and the range for SOX17 was 1.17–1.43.

Aneurysm Rupture

There were a total of 2061 IA rupture patients and 10,607 controls. Three studies used the same sample of patients to analyze different genes for association with IA.^[43,44] Polymorphisms from 19 different genes were investigated. None of the genes were investigated by more than one study.

Only 5 of the genes had polymorphisms with significant associations. These polymorphisms come from 9p21, coagulation factor XIII, MAPKAP1, and eNOS. The 9p21

Table 1: Aneurysm formation

Study	Year	Total patients	IA patients	Gene(s)	Gene function	Variants tested	Greatest reported OR	95% CI	P
Akiyama <i>et al.</i> ^[19]	2010	1973	1069	IQSEC1	Cell adhesion activator protein ARF-GEP100	Rs9864101	1.49	1.23-1.80	<0.001
						Rs7550260	1.32	1.15-1.50	<0.001
						Rs7781293	1.32	1.16-1.50	<0.001
						Rs4628172	1.30	1.14-1.48	<0.001
Chen <i>et al.</i> ^[20]	2012	786	298	COL3A1	Type III collagen	Rs1930095	1.44	1.22-1.71	<0.001
						Rs1800255	1.71	1.19-2.45	0.004
Foroud <i>et al.</i> ^[21]	2012	3166	1483	SAP130	None	rs11693075	1.26		<0.001
						rs10757270	1.30		<0.001
						rs6475606	1.35	1.22-1.52	<0.001
						rs10757272	1.33		<0.001
						rs4977574	1.32		<0.001
						rs2891168	1.33		<0.001
						rs1333048	1.32		<0.001
						rs911774	1.18		0.012
						rs11112585	1.22		0.011
						rs2374513	1.28		0.002
Foroud <i>et al.</i> ^[22]	2014	5156	2617	CDKN2BAS	Associated with atherosclerotic disease	rs10733376	1.34	1.23-1.45	<0.001
						rs10230207			<0.001
						rs1333040	1.28	1.04-1.57	0.02
						Rs42524	1.83	1.1-3.0	0.02
Hashikata <i>et al.</i> ^[23]	2010	142	96	9p21 (CDKN2BAS)	Associated with atherosclerotic disease	Rs1800238	1.74	0.31-9.7	0.62
						Rs2621215	1.49	0.89-2.49	0.13
Gläser <i>et al.</i> ^[24]	2014	269	269	COL1A2	Type 1 collage	Rs2621215	1.49	0.89-2.49	0.13
						Rs1333040	1.43	1.24-1.66	<0.001
Nakaoka <i>et al.</i> ^[25]	2010	1680	981	9p21 (CDKN2BAS)	Associated with atherosclerotic disease	rs2891168	1.32	1.15-1.52	<0.001
						rs2383207	1.34	1.16-1.55	<0.001
						rs10757278	1.33	1.16-1.52	<0.001
						Rs2621215GG	7.89	0.44-140.93	0.057
Joo <i>et al.</i> ^[26]	2009	509	320	COL1A2	Type I collagen	27VNTR			0.999
Kim <i>et al.</i> ^[27]	2011	270	149	eNOS	Endothelial nitric oxide synthase	T786C			0.999
						G894T	0.832	0.429-1.611	0.585
						Rs741846	1.337	1.10-1.63	0.004
Krischek and Inoue ^[28]	2010	2198	963	JDP2	Transcription repressor	Rs175646	1.505	1.09-2.09	0.014
						Rs8215	1.269	1.04-1.55	0.019
						Rs3212227AC/CC	2.09	1.29-3.38	<0.001
Li <i>et al.</i> ^[29]	2012	422	164	IL-12A/B	Interleukin 12	Rs4938723CC	0.28	0.11-0.73	0.006
Li <i>et al.</i> ^[30]	2012	590	164	miR-34b/c	Micro RNA	Rs1800956G	1.56	1.08-2.26	0.019
Lin <i>et al.</i> ^[31]	2014	863	313	D336H	Endoglin	GG	3.35	1.65-6.82	0.001
Liu <i>et al.</i> ^[32]	2012	440	220	IL-6-572	IL-6				
Low <i>et al.</i> ^[33]	2011	2885	2050	LIMK1	Kinase for actin cytoskeleton	Rs6460071	1.24	1.06-1.45	0.004
						Rs243847	1.16	1.05-1.28	0.05
						Rs243865	1.23	1.02-1.5	0.035
						Rs1799724	1.17	1.03-1.32	0.031
Low <i>et al.</i> ^[34]	2012	6867	1383	EDNRA	Endothelin-1 Receptor	Rs6842241	1.25	1.16-1.34	<0.001
						Rs10757272	1.21	1.13-1.30	<0.001
						Rs671	1.240	1.148-1.338	<0.001
Ruigrok <i>et al.</i> ^[35]	2009	1440	632	CSPG2	Versican (ECM structure)	Rs251124	1.29	1.12-1.48	<0.001
						Rs3767137	1.22	1.08-1.39	0.002
Ruigrok <i>et al.</i> ^[36]	2012	1815	791	TGFBFR1	TGF-β receptor	Rs1626340	1.24	1.05-1.46	0.01
						Rs10819634	1.23	1.03-1.46	0.02
Suo <i>et al.</i> ^[37]	2014	751	308	KLK	Kallikrein (serine protease; basement membrane components, remodelling)	Rs1722561	0.71	0.53-0.95	0.023
						Rs1701946	0.78	0.57-1.06	0.115

Contd...

Table 1: Contd...

Study	Year	Total patients	IA patients	Gene(s)	Gene function	Variants tested	Greatest reported OR	95% CI	P
Yasuno <i>et al.</i> ^[38]	2010	20072	5891	RBBP8	Retinoblastoma binding protein 8	Rs11661542	1.22	1.15-1.28	<0.001
				STAR13/KL	StAR-related lipid transfer; suppresses cell proliferation	Rs9315204	1.20	1.13-1.28	<0.001
				CNNM2	Cyclin M2	Rs12413409	1.29	1.19-1.40	<0.001
				SOX17	Transcription factor	Rs9298506	1.28	1.20-1.38	<0.001
Yasuno <i>et al.</i> ^[39]	2011	20162	5891	CDKN2A/B	Associated with CAD	Rs1333040	1.31	1.25-1.39	<0.001
				EDNRA	Endothelin-1 receptor	Rs6841581	1.22	1.14-1.31	<0.001
				NDUFA12/INR2C1/FGD6/VEZT	Ubiquinone 1 alpha-12, nuclear receptor	Rs6538595	1.16	1.10-1.23	<0.001
				RRBP1	Ribosome binding protein	Rs1122274	1.20	1.11-1.28	<0.001

Absence of data indicates that data were not reported numerically. ECM – Extracellular matrix; CAD – Coronary artery disease; TGF- β – Transforming growth factor-beta; TNF- α – Tumor necrosis factor-alpha; CI – Confidence interval; OR – Odds ratio; IA – Intracranial aneurysms; IL-6 – Interleukin-6

Table 2: Aneurysm rupture

Study	Year	Total patients	SAH patients	Gene(s)	Gene function	Variants tested	Greatest reported OR	95% CI	P
Adamski <i>et al.</i> ^[40]	2009	745	288	GpIIa	Platelet mediated thrombosis receptor	GpIIa A1/A2	0.922	0.783-1.085	
Adamski <i>et al.</i> ^[41]	2014	817	392	AGTR1/A116C	Angiotensin II type 1 receptor	A116C			Nonsignificant
Hanson <i>et al.</i> ^[42]	2013	863	183	ADAMTS13	Thrombus inhibition (cleaves vWF)	Rs2285489	0.77	0.60-1.00	
						Rs739469	0.71	0.40-1.27	
						Rs2301612	0.96	0.66-1.40	
						Rs652600	1.20	0.68-2.12	
Olsson <i>et al.</i> ^[43]	2011	549	183	9p21	Associated with atherosclerotic disease	Rs4962153	0.79	0.44-1.42	
						Rs10965227	0.83	0.58-1.19	0.31
						Rs1547705	1.39	0.91-2.11	0.12
						Rs7857345	0.80	0.59-1.07	0.14
Olsson <i>et al.</i> ^[44]	2012	549	183	MMP2		Rs1333045	0.78	0.59-1.02	0.07
						Rs10757278	1.42	1.08-1.87	0.01
						Rs1537378	0.8	0.60-1.07	0.14
						Rs243864			
				MMP9		Rs865094			
						Rs12934241			
						Rs243847			
						Rs2287074			
Pera <i>et al.</i> ^[45]	2012	857	276	IL-6	Inflammatory cytokine	Rs1163996			
						Rs11541998			
						Rs7201			
						Rs17576			
Ruigrok <i>et al.</i> ^[46]	2010	1133	208	Factor V Leiden Prothrombin MTHFR	Increased thrombosis Coagulation	Rs2236416			
						Rs20544	1.6	1.0-2.6	
						Rs3918256	1.6	1.0-2.6	
						Rs3787268			
Pera <i>et al.</i> ^[45]	2012	857	276	IL-6	Inflammatory cytokine	IL-6-174G>C Recessive model	1.15	0.78-1.68	0.48
						IL-6-174G>C Dominant model	0.97	0.63-1.48	0.87
Ruigrok <i>et al.</i> ^[46]	2010	1133	208	Factor V Leiden Prothrombin MTHFR	Increased thrombosis Coagulation	G1691A GA, AA	0.9	0.5-1.8	
						G20210A GA, AA	1.5	0.6-3.5	
						C677T TT	1.2	0.3-2.0	

Contd...

Table 2: Contd...

Study	Year	Total patients	SAH patients	Gene(s)	Gene function	Variants tested	Greatest reported OR	95% CI	P				
Staalsø <i>et al.</i> ^[47]	2011	674	176	Factor XIII subunit A	Coagulation	Val34Leu ValLeu, LeuLeu	0.9	0.7-1.2					
						Tyr204Phe TyrPhe, Phe/Phe	1.7	0.9-2.9					
						Pro564Leu ProLeu, LeuLeu	1.2	0.8-1.6					
				Factor XIII subunit B	Coagulation	His95Arg HisArg, ArgArg	1.5	1.0-2.2	0.04				
						ACE	ACE	Rs4291	0.99	0.78-1.28	0.59		
				Staalsø <i>et al.</i> ^[48]	2014	831	333	eNOS3	Endothelial nitric oxide synthase	Rs4295	0.93	0.71-1.22	0.41
										Rs4305	0.95	0.73-1.25	0.93
Rs4311	1.02	0.79-1.32	0.29										
Rs4331	1.16	0.90-1.50	0.49										
I/D	1.08	0.84-1.38	0.78										
Rs4343	1.12	0.87-1.43	0.62										
Rs1800779	1.2	0.9-1.7	0.11										
Yoshida <i>et al.</i> ^[49]	2010	4304	205	COL6A3	Collagen	Rs2070744	1.2	0.9-1.6	0.2				
						Rs1799983	1.0	0.8-1.4	0.6				
						27-bp-VNTR polymorphism	1.5	1.1-2.0	0.02				
						Rs11690358			0.12				
						Rs3111754			0.47				
						Rs10986769	1.58	1.06-2.31	0.02				
						Rs4653579			0.22				
Rs199515			0.50										
Rs8053843			0.28										

SAH – Sub-arachnoid haemorrhage; CI – Confidence interval; OR – Odds ratio; IL-6 – Interleukin-6; vWF – Von Willebrand factor

polymorphism was found to have an OR of 1.42 ($P = 0.01$), the Factor XIII subunit B polymorphism had OR = 1.5 (0.04), MAPKAP1 had an OR of 1.58 ($P = 0.02$), and eNOS had an OR of 1.5 ($P = 0.02$).

Discussion

This investigation found that multiple studies have shown statistically significant association between IA formation and variants of the genes CDKN2, SOX17, and EDNRA. The association of these genes with IA formation across studies leads to the next possible query of how they are associated. Furthermore, only a few genes are associated with aneurysmal rupture (9p21, coagulation factor XIII, MAPKAP1, and eNOS).

Research into aneurysm wall morphology has shown that IAs display fewer layers of the vessel wall and less cell density than normal vasculature.^[52] Challa and Han demonstrated using simulations that decreased vessel wall thickness would lead to greater stress, a known cause of IA.^[53,54] Conversely, however, at least, one study has shown that there is a significant association of IA with increased vessel wall thickness through carotid intima-medial thickness testing, with the researchers noting that aneurysm patients had decreased circumferential stress and significantly lower elasticity when compared to controls.^[55] This may indicate that aneurysm formation is not necessarily due to either increased or decreased thickness but

possibly heterogeneous vessel wall structure. Simulations have also shown that stress was also increased in areas with heterogeneous thickness,^[53] an effect may more pronounced in areas such as arterial bifurcations which receive the greatest shear stress.^[56] A study by Nakatomi *et al.* on intracranial fusiform aneurysms noted that IA occurrence can be connected with not only breakdown of the internal elastic lamina, but also to proliferation after initial damage has occurred.^[57] A connection between IA formation and CDKN2, SOX17, and EDNRA could genetically link heterogeneous vessel structure and the mechanisms mentioned.

CDKN2 is located at 9p21 and variations may be involved in coronary artery disease or aortic aneurysms.^[25] In our literature review, polymorphisms of this gene were found to have associations with IA in multiple studies with a range of OR from 1.21 to 1.43.^[21,23,25,34,38] Although the exact relationship is unknown it can be theorized. CDKN2BAS is an antisense region of the DNA bordered by genes for CDK inhibitors, which prevent vascular smooth muscle from proliferating. It is believed that dysfunction of the CDK inhibitors could lead to vascular wall abnormalities and thus to IA aneurysm formation.^[58] If the proposed function of CDKN2 is correct, abnormalities could lead to up- or down-regulation of proliferation and, therefore, a heterogeneous wall thickness. Abnormal wall thickness would, in turn, increase the risk of IA according to the previously mentioned work by Nakatomi

et al. and Maltete *et al.*, and would explain the relationship between CDKN2 and IA shown by multiple studies in this investigation.^[55,57]

EDNRA acts as a receptor for Endothelin-1, which causes both vasoconstriction and proliferation of vascular smooth muscle cells. The theorized purpose of EDNRA is to modulate the effects of hemodynamic stress.^[34] The polymorphisms of EDNRA associated with IA formation identified in the present investigation may result in the inability of the vascular smooth muscle to compensate against the shearing forces previously described. Decreased vascular compensation has also been discussed by Maltete *et al.* in which decreased vascular compliance associated in IA patients was believed to contribute to their formation.^[55] SOX17, another gene shown to be associated with IA by two studies in this investigation, also contributes to endothelial maintenance^[51] and, therefore, may also be involved in a homeostatic mechanism. While the exact effect of these CDKN2, EDNRA and SOX17 polymorphisms on IA is uncertain, it seems that vessel wall heterogeneity may lead to increased IA formation either through weakening the overall structure of the vessel wall or by limiting its ability to compensate against stress.

When compared to IA formation, our study reveals less information regarding genetics associations of aneurysm rupture and SAH. Only a single study has demonstrated an association between CDKN2 and SAH.^[43] Unfortunately, a more definitive link cannot be reached. If aneurysm formation and rupture exist along a continuum of structural change as theorized by Chalouhi *et al.*,^[54] then perhaps this explains the effect of CDKN2 on aneurysm rupture. However, it is important to note that the same study which noted an association between the 9p21 locus and SAH did not find such an association with five other CDKN2 polymorphisms that they tested.^[43] A single study noted an association between aneurysm rupture and Factor XIII Subunit B.^[46] An association was also found in a different study with a polymorphism for the MAPKAP gene which is involved in cell signaling.^[49] The relationship between either of these genes and SAH has not been fully researched, and we were unable to find information about possible mechanisms for aneurysm rupture.^[46,49]

Our analysis highlights the possibly critical yet very limited amount of information available on the impact genetic factors may have on IA formation and rupture. A paucity of information exists on the exact mechanisms by which these genes affect aneurysm formation or rupture, and much of the information is theoretical. If the mechanisms of genetic involvement were laid out, perhaps new screening methods would be able to identify individuals at greater risk of aneurysm formation. More importantly, development of a risk stratification tool for aneurysm rupture and SAH would allow for early intervention.

With the identification of a reliable genetic target in IA patients, novel treatment strategies could be devised to exploit a specific genetic locus. In a rabbit model, the progression of abdominal aortic aneurysms was able to be significantly reduced using deoxynucleotides targeted at the specific gene, NFκB.^[59] Although this study was conducted in a nonhuman model, and not on IA specifically, it does show the potential of genetically targeted therapy to affect the development of aneurysms. It has been proposed that endovascular treatment of IA could be augmented by gene transfer using vectors embedded in coils.^[60] Further studies should be carried out in the future identify a gene or genes strongly associated with IA or SAH to advance treatment strategies.

Conclusion

Our review found that IA formation and SAH was associated with several possible genetic factors. The most studied gene and the strongest association was 9p21/CDKN2, which is involved in vessel wall remodeling. Other possible genes that may contribute to IA formation include EDNRA and SOX17; however, these factors were not studied as robustly as CDKN2. Overall, information regarding genetics of IA formation and SAH is lacking. Genetics are most likely one of many factors contributing to aneurysm formation and rupture. The contributions of blood flow dynamics and comorbidities as mentioned previously, cannot be ignored. While these elements are important to development and rupture of aneurysms, genetic influence may predispose certain patients to the formation of aneurysms and eventual rupture. Further research into the genetic factors responsible for structural remodeling and inflammatory response to endothelial injury that occur in IA and SAH is needed to better identify at-risk patients and develop novel gene-based therapies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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