

Genetic risk factors for intracranial aneurysms

A meta-analysis in more than 116,000 individuals

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ABSTRACT

Objective: There is an urgent need to identify risk factors for sporadic intracranial aneurysm (IA) development and rupture. A genetic component has long been recognized, but firm conclusions have been elusive given the generally small sample sizes and lack of replication. Genome-wide association studies have overcome some limitations, but the number of robust genetic risk factors for IA remains uncertain.

Methods: We conducted a comprehensive systematic review and meta-analysis of all genetic association studies (including genome-wide association studies) of sporadic IA, conducted according to Strengthening the Reporting of Genetic Association Studies and Human Genome Epidemiology Network guidelines. We tested the robustness of associations using random-effects and sensitivity analyses.

Results: Sixty-one studies including 32,887 IA cases and 83,683 controls were included. We identified 19 single nucleotide polymorphisms associated with IA. The strongest associations, robust to sensitivity analyses for statistical heterogeneity and ethnicity, were found for the following single nucleotide polymorphisms: on chromosome 9 within the cyclin-dependent kinase inhibitor 2B antisense inhibitor gene (rs10757278: odds ratio [OR] 1.29; 95% confidence interval [CI] 1.21–1.38; and rs1333040: OR 1.24; 95% CI 1.20–1.29), on chromosome 8 near the SOX17 transcription regulator gene (rs9298506: OR 1.21; 95% CI 1.15–1.27; and rs10958409: OR 1.19; 95% CI 1.13–1.26), and on chromosome 4 near the endothelin receptor A gene (rs6841581: OR 1.22; 95% CI 1.14–1.31).

Conclusions: Our comprehensive meta-analysis confirms a substantial genetic contribution to sporadic IA, implicating multiple pathophysiologic pathways, mainly relating to vascular endothelial maintenance. However, the limited data for IA compared with other complex diseases necessitates large-scale replication studies in a full spectrum of populations, with investigation of how genetic variants relate to phenotype (e.g., IA size, location, and rupture status). *Neurology*[®] 2013;80:2154–2165

GLOSSARY

ACE = angiotensin-converting enzyme; **ANRIL** = antisense noncoding RNA in the INK4 locus; **CI** = confidence interval; **CGAS** = candidate gene association study; **EDNRA** = endothelin receptor type A; **GWAS** = genome-wide association studies; **IA** = intracranial aneurysm; **IL** = interleukin; **LD** = linkage disequilibrium; **MMP** = matrix metalloproteinase; **OR** = odds ratio; **SAH** = subarachnoid hemorrhage; **SNP** = single nucleotide polymorphism.

Intracranial aneurysms (IAs) are present in 2%–5% of the general population; approximately 0.7%–1.9% of cases rupture, causing subarachnoid hemorrhage (SAH).¹ The annual incidence of SAH is 8–9 in 100,000, yet because of the high risk of death or severe disability² and younger age at onset compared with other stroke types (40–65 years),³ SAH has a disproportionately large socioeconomic impact.

SAH has been associated with common modifiable risk factors, including hypertension, smoking, and alcohol intake.^{4–6} However, a genetic component has long been recognized; for example, first-degree relatives of patients with aneurysmal SAH have a 4- to 7-fold increased risk of being affected compared with the general population.^{7,8} Candidate gene association studies (CGAS) of sporadic IA have identified numerous potential risk loci, but these studies have been limited by small sample

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sizes and lack of replication. More recently, genome-wide association studies (GWAS) have identified novel genetic loci strongly associated with IAs,^{9–14} but these still explain only a fraction of the genetic risk.

Thus, the number of true genetic risk factors and the strength of their associations with IAs remain uncertain. The pooling of data from all genetic association studies allows risk estimates to be determined with more precision than is possible from any single study and allows assessment of robustness to statistical heterogeneity and population ethnicity differences across studies. We therefore undertook a comprehensive systematic review and meta-analysis of all published CGAS and GWAS of sporadic IA, including sensitivity analyses for statistical heterogeneity and ethnicity.

METHODS Our meta-analysis was conducted in accordance with the Human Genome Epidemiology Network guidelines¹⁵ and followed published recommendations to improve the quality of meta-analyses of genetic association studies.¹⁶ We assessed the quality of reporting of genotyping on the basis of the Strengthening the Reporting of Genetic Association Studies statement.¹⁷

Search strategy. Electronic databases (PubMed, EMBASE, and Google Scholar) were used to retrieve potentially relevant articles on human genetic studies of IAs and SAH that had been published up to December 2012. Search terms used under the Medical Subject Headings were aneurysm(s), intracranial aneurysm(s), subarachnoid hemorrhage, genetics, SNPs [single nucleotide polymorphisms], polymorphism, GWAS, and linkage and candidate gene(s).

Articles in all languages were searched (see figure 1 for a flow diagram of the search strategy) and translated as necessary. After relevant articles were retrieved, references were also checked for other potentially relevant articles not found in the initial search.

Selection criteria. We included cohort or case-control studies evaluating associations of genetic polymorphisms with proven IA (using CT/MR angiograms or digital subtraction angiography), including unrelated individuals from CGAS and GWAS, in all ethnicities. Where duplicate datasets or cohorts existed, only the largest study was included. All single nucleotide polymorphisms (SNPs) evaluated in at least 2 published studies (CGAS or GWAS) were included in meta-analysis. Exclusion criteria were a history of inherited conditions associated with IAs, e.g., adult polycystic kidney disease or Ehlers-Danlos syndrome.

Data extraction. Data were extracted by 2 of the authors (V.S.A. and D.J.W.), and differences were resolved by consensus. Where available, genotype frequencies for each SNP were recorded. Where they were unavailable, we estimated the number of cases per genotype category by using published information on risk allele frequencies and odds ratios (ORs) for IA.

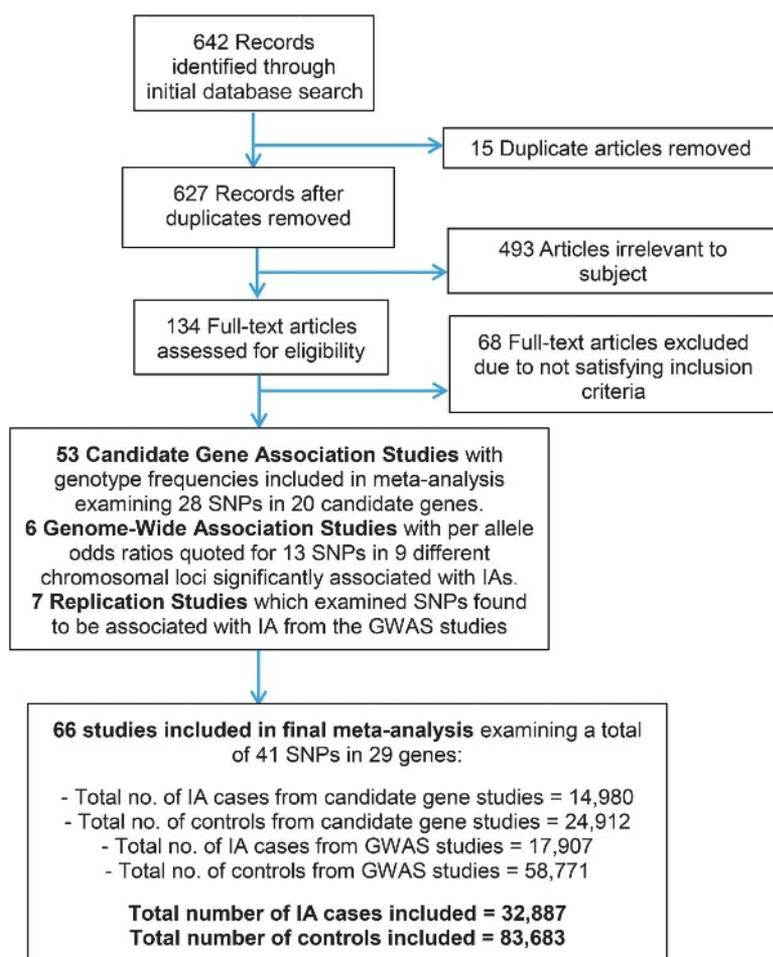
Statistical analysis. For each genetic polymorphism with more than one publication, meta-analysis was performed to determine a pooled OR and 95% confidence intervals (CIs) by using a fixed-effect model (Mantel-Haenszel method). Interstudy heterogeneity *p* values were measured from Cochran Q test and quantified by using Higgins *I*² statistic. SNP associations showing significant interstudy heterogeneity (interstudy heterogeneity *p* values <0.05 and *I*² >50%) were examined under a random-effects (DerSimonian and Laird) model, and, where appropriate, subjected to sensitivity analysis to determine the effect of individual studies on the pooled OR. Ethnic subgroup analysis was also performed where appropriate.

All genetic models (dominant, recessive, and additive) were assessed in studies recording genotype frequencies. Bonferroni correction was applied for multiple testing (*p* < 0.01). In studies not recording genotype frequencies, per-allele (additive) ORs were pooled with calculation of CIs. Controls were checked to be in Hardy-Weinberg equilibrium for each study before meta-analysis.

Publication bias was assessed by using the Egger regression asymmetry test and visualization of funnel plots. Review Manager (RevMan) version 5.2 from the Cochrane Collaboration (London, UK), 2011, and Comprehensive Meta-Analysis (2.2) from Biostat (Tampa, FL) were used to create the forest plots and perform sensitivity and publication bias analysis.

RESULTS Our search identified 642 articles, of which 134 articles met initial inclusion criteria. Two studies published in Chinese were translated. After screening for duplication and eligibility, data from 66 case-control studies (60 CGAS and 6 GWAS) were included.

Figure 1 Flow chart illustrates the number of studies evaluated in this meta-analysis



GWAS = genome-wide association studies; IA = intracranial aneurysm; SNP = single nucleotide polymorphism.

Genotype and allele frequencies were reported in 48 publications; the remaining 18 reported additive ORs. In total, 32,887 cases and 83,683 control subjects were included, evaluating 41 polymorphisms in 29 genes (figure 1). The studies encompassed mainly white European, Chinese, and Japanese populations. Risk allele frequencies and control Hardy-Weinberg equilibrium status for each study of all SNPs meta-analyzed are shown in table e-1 on the *Neurology*[®] Web site at www.neurology.org.

We identified 19 SNPs (from CGAS and GWAS) that were significantly associated with IAs in at least one genetic model (table 1). The most robust associations were seen in 11 of 12 SNPs discovered from GWAS (table 1), with the strongest associations for loci on chromosome 9 (rs1333040 and rs10757278), chromosome 8 (rs9298506 and rs10958409), and chromosome 4 (rs6841581; figure 2). Other GWAS loci variants associated with IAs included 9p21.3 (rs2891168), 2q33 (rs1429412 and rs700651), 7q13 (rs4628172), 12q22 (rs6538595), and 20p20.1 (rs1132274; table 1 and figures e-1 and e-2).

Eight SNPs from CGAS were significantly associated with IAs; *SERPINA3* (rs4934) and 2 variants relating to collagen genes (*COL1A2* [rs42524 G>C] and *COL3A1* [rs1800255 G>A]) showed the most robust associations. The remaining significantly associated CGAS SNPs included heparan sulfate proteoglycan 2 (rs3767137), versican (rs251124 and rs173686), angiotensin-converting enzyme (*ACE*) I/D, and interleukin 6 (*IL6*) G572C (table 1, figure 3, and figure e-2).

SNPs demonstrating statistical heterogeneity. Nine of the 19 significantly associated SNPs (*SERPINA3*, *ACE* I/D, *IL6* G572C, chondroitin sulfate proteoglycan 2 [rs173686, rs1333040, rs700651, rs9298506, rs10958409, and rs4628172]) showed significant statistical heterogeneity; random-effects and sensitivity analyses were possible only for the 7 variants reported in more than 2 publications (table 2). After sensitivity analysis, the *SERPINA3*, *ACE* I/D, and *IL6* G572C SNPs (figure 3F) derived from CGAS no longer showed an association with IA.

Ethnicity analysis. Nine SNPs (2 from CGAS and 7 from GWAS) were subjected to subgroup analysis to determine the effect of ethnicity (table 3 and figures e-3 to e-6). Associations with IA in Japanese, Chinese, and white populations were compared for each SNP, after which 5 of these 9 SNPs (all from GWAS) remained robustly associated with IA in all groups (table 3).

Publication bias. Inspection of funnel plots and calculation of Egger *p* values confirmed that none of the SNPs (CGAS or GWAS) associated with IAs (table 1) showed publication bias. See figures e-7 to e-11 for funnel plots of all SNPs (CGAS and GWAS) associated with IA.

CGAS not confirming associations with IAs. Twenty-two candidate SNPs reported in more than one study were not associated with IAs after meta-analysis (table e-2), including the following: endothelial nitric oxide synthase variable number tandem repeat 4a/4b, endothelial nitric oxide synthase T786C, endothelial nitric oxide synthase G894T, endoglin intron 7 Wt/Ins, matrix metalloproteinase (MMP)-3 5A/6A, elastin intron 20T>C, elastin intron 23C>T, IL-1 β C5111T, IL-6 G174C, plasminogen activator inhibitor-1 4G/5G, glycoprotein IIIa A1/A2, factor XIII valine/leucine, *APOE* ϵ 2 and ϵ 4, *COL4A1* C>T (rs3783107), fibrillin-2 C>G (rs331079), MMP-2 C>T (rs243865), MMP-9 C1562T (rs3918242), *COL3A1* (rs2138533C>T and rs11887092A>G), rs10757272C>T, and rs11661542A>C.

DISCUSSION This comprehensive systematic review and meta-analysis has identified 19 SNPs associated with IAs among 32,887 cases and 83,683 controls. The variety of genes implicated by these SNPs suggests that multiple pathophysiologic pathways, mainly involved in vascular endothelial maintenance and extracellular matrix integrity, are likely to contribute to IA development and rupture. The most robust SNPs identified arose from variants on chromosomes 4, 8, and 9, derived from GWAS and confirmed by subsequent replication case-control studies.

Genetic variants associated with IAs identified by GWAS. SNPs with potential roles in vascular endothelial maintenance. The SNP rs1333040 located on chromosome 9p21.3 in the cyclin-dependent kinase inhibitor 2B antisense gene was strongly associated with IAs. Two major linkage disequilibrium (LD) blocks exist within the 9p21.3 locus: one associated with vascular diseases and the other associated with diabetes. This locus is associated with a wide spectrum of arterial disorders, including coronary artery disease and abdominal aortic aneurysms,¹⁸ raising the possibility that there are as yet unidentified common processes involved in all these common cardiovascular pathologies. The cyclin-dependent kinase inhibitor 2B antisense gene, on intron 12, is associated with cell cycle signaling, although its exact biological roles are not fully understood.^{9,10} Association of the rs1333040 SNP with IAs was found to be independent of smoking and hypertension in one study.¹⁹ In multivariable analysis, this SNP was preferentially associated with posterior communicating artery aneurysms, providing preliminary evidence that aneurysm site could be related to genetic factors.¹⁹ However, larger cohorts will need to be studied in addition to scanning the entire region to check which SNPs are in LD with the rs1333040-T allele and whether they have any cumulative (epistatic) effect on IA phenotype, including location.

Table 1 SNPs associated with IAs

Gene/locus	SNP	Genetic model	No. studies	Cases	Controls	FE OR (95% CI)	$P_{\text{corrected}}$ (Bonferroni)	P_{Het} (I^2)	Robust association after random effects/sensitivity analyses	Potential biological mechanism of association with IA
Genome-wide association study SNP associations										
9p21.3	C>T (rs1333040)	Additive	12 ^{9-11,13,14,19,24}	11,949	29,014	1.24 (1.2-1.29)	9.83×10^{-08}	5.40×10^{-08} (80%)	✓	Vascular endothelium
9p21	A>G (rs10757278)	Additive	7 ^{18-21,24}	3,394	17,075	1.29 (1.21-1.38)	1.59×10^{-13}	0.84 (0%)	NA	Vascular endothelium
8q11	A>G (rs9298506)	Additive	8 ^{9,10,13,24}	9,246	26,331	1.21 (1.15-1.27)	1.55×10^{-13}	1.90×10^{-07} (84%)	✓	Vascular endothelium
8q11	A>G (rs10958409)	Additive	8 ^{9-11,13,20,24}	9,873	27,029	1.20 (1.15-1.26)	1.78×10^{-15}	6.87×10^{-05} (76%)	✓	Vascular endothelium
4q31.23	A>G (rs6841581)	Additive	6 ¹²	4,370	14,181	1.22 (1.14-1.31)	1.95×10^{-8}	0.39 (4%)	NA	Vascular endothelium
9p21.3	C>G (rs2891168)	Additive	2 ^{14,19}	2,076	1,985	1.32 (1.21-1.44)	9.84×10^{-10}	0.98 (0%)	NA	Vascular endothelium
2q33	G>A (rs1429412)	Additive	4 ^{9,11,24}	2,675	7,632	1.20 (1.12-1.30)	1.07×10^{-06}	0.30 (18%)	NA	Unknown
2q33	G>A (rs700651)	Additive	6 ^{9,13,20,24}	4,283	13,236	1.11 (1.06-1.18)	7.13×10^{-05}	1.17×10^{-02} (66%)	✓	Unknown
7q13	G>T (rs4628172)	Additive	2 ^{11,13}	2,443	6,376	1.11 (1.03-1.19)	4.04×10^{-03}	4.71×10^{-03} (87%)	NA	Unknown
12q22	G>A (rs6538595)	Additive	6 ¹²	4,370	14,181	1.16 (1.10-1.23)	1.12×10^{-7}	0.98 (0%)	NA	Unknown
20p12.1	G>A (rs1132274)	Additive	5 ¹²	4,370	14,181	1.19 (1.11-1.28)	8.29×10^{-7}	0.52 (0%)	NA	Unknown
Candidate gene SNP associations										
SERPINA3	A>G (rs4934)	Dominant	3 ⁴⁰⁻⁴²	892	1,029	2.22 (1.68-2.94)	<0.00001	<0.00001 (97%)	×	Extracellular matrix
		Recessive				0.80 (0.49-1.31)	0.25	0.04 (69%)		
		Additive				1.27 (1.07-1.50)	0.0002	<0.00001 (94%)		
COL1A2	G>C (rs42524)	Dominant	3 ⁴³⁻⁴⁵	812	806	1.77 (1.14-2.75)	0.0009	0.09 (58%)	NA	Extracellular matrix
		Recessive				1.14 (0.16-7.94)	0.86	0.31 (4%)		
		Additive				1.69 (1.11-2.57)	0.001	0.06 (64%)		
COL3A1	G>A (rs1800255)	Dominant	2 ^{46,47}	546	2,235	1.55 (1.21-2.00)	<0.00001	0.25 (23%)	NA	Extracellular matrix
		Recessive				1.31 (0.72-2.38)	0.25	0.70 (0%)		
		Additive				1.40 (1.14-1.72)	<0.0001	0.26 (21%)		
HSPG2	A>G (rs3767137)	Additive	2 ^{31,32}	1,316	1,742	1.22 (1.08-1.39)	0.002	0.122 (58%)	NA	Extracellular matrix
Versican (CSPG2)	C>T (rs251124)	Additive	3 ³⁰⁻³²	1,489	1,687	1.25 (1.1-1.41)	0.0007	0.201 (38%)	NA	Extracellular matrix
Versican (CSPG2)	A>G (rs173686)	Additive	2 ^{30,31}	857	879	1.23 (1.05-1.43)	0.008	0.013 (84%)	NA	Extracellular matrix
ACE	I/D	Dominant	5 ⁴⁸⁻⁵²	767	1,172	0.82 (0.61-1.12)	0.66	0.002 (76%)	×	Vascular endothelium
		Recessive				1.39 (1.05-1.84)	0.002	0.01 (69%)		
		Additive				1.23 (1.07-1.40)	0.003	0.47 (0%)		

Continued

Table 1 Continued

Gene/locus	SNP	Genetic model	No. studies	Cases	Controls	FE OR (95% CI)	$P_{\text{corrected}}$ (Bonferroni)	P_{het} (I^2)	Robust association after random effects/sensitivity analyses	Potential biological mechanism of association with IA
<i>IL6</i>	G572C	Dominant	5 ^{36,37,53-55}	912	3,410	0.68 (0.48–0.96)	0.004	<0.00001 (92%)	×	Inflammatory mediator
		Recessive				0.47 (0.34–0.65)	<0.00001	<0.00001 (94%)		
		Additive				0.61 (0.49–0.75)	<0.00001	<0.00001 (95%)		

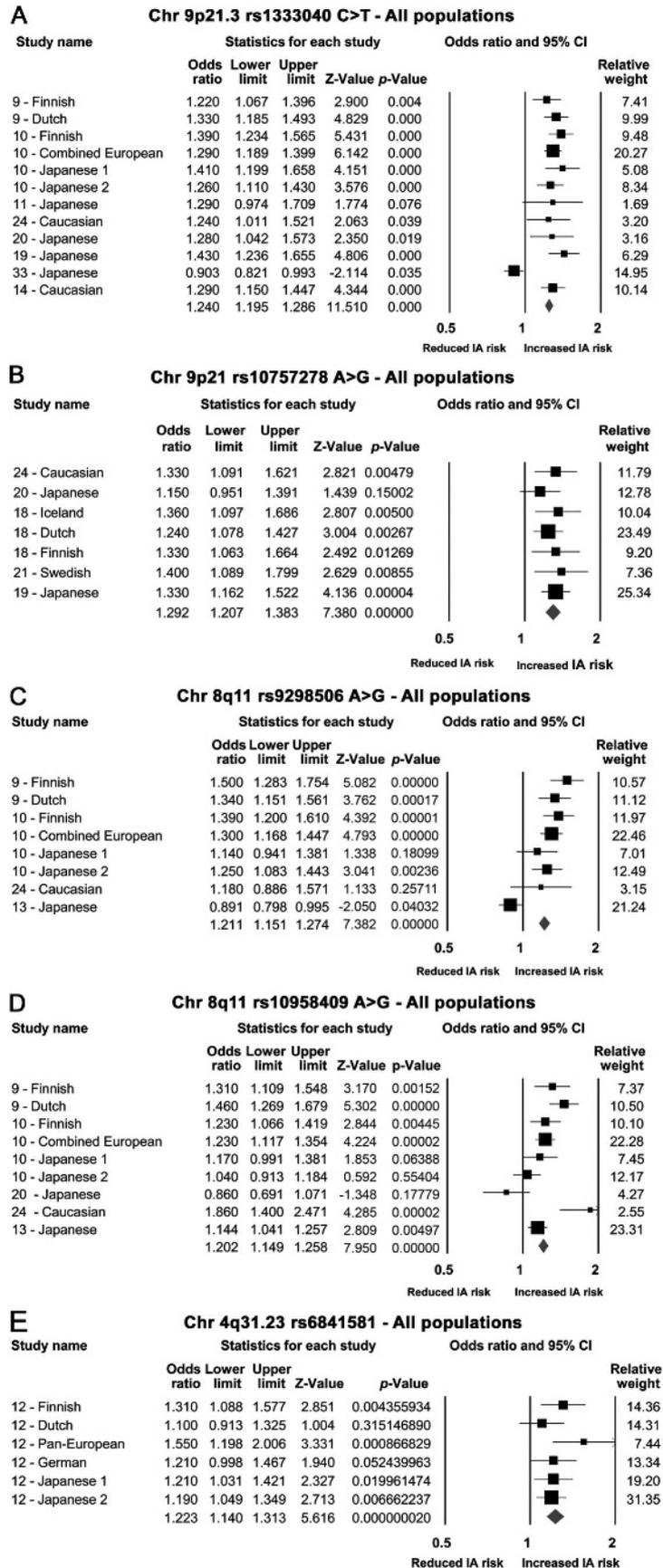
Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; CSPG = chondroitin sulfate proteoglycan; FE = fixed-effects model; HSPG = heparan sulfate proteoglycan; I^2 = Higgins statistic demonstrating degree of interstudy heterogeneity; IA = intracranial aneurysm; IL = interleukin; NA = not applicable; OR = odds ratio; P_{het} = interstudy heterogeneity p value; SNP = single nucleotide polymorphism. ✓ = SNP robustly associated with IA following sensitivity and random-effects analysis; × = SNPs not robustly associated with IA following sensitivity analysis and random-effects analysis.

The SNP rs10757278 on chromosome 9p21.3, located in a noncoding RNA region called *ANRIL* (antisense noncoding RNA in the *INK4* locus), showed robust association with IAs, but its function remains unclear. Moreover, the observed association of rs10757278 with IA may arise from moderate LD with the known IA risk variant rs1333040 SNP ($r = 0.59$), from which it is approximately 41 kbp upstream.²⁰ However, these 2 SNPs were not in strong LD in a Japanese population, raising the possibility of a smaller LD block associated with IA. In a Japanese study,¹⁹ haplotype analysis of both risk alleles of these SNPs demonstrated significant association with IAs (OR 1.56; 95% CI 1.32–1.85; $p = 2.9 \times 10^{-07}$). Functional studies show altered *ANRIL* expression as a result of variations within the 9p21.3 region,¹⁴ with reduced expression of RNA encoded by *CDKN2A* and *CDKN2B* in mice¹⁴; these 2 genes, adjacent to the 9p21 region, encode tumor-suppressor proteins (p14–16), which are involved in cell proliferation.²¹ Moreover, p14 levels correlate with *ANRIL* activity and modulate MMP-3 levels, which may influence extracellular matrix repair.²¹

In the most recent GWAS¹⁴ in a Caucasian population of familial and sporadic IA, 6 SNPs, also located in the 9p21.3 region, were associated with IA; one of these (rs6475606) achieved GWAS-level statistical significance (OR 1.34; $p = 4.29 \times 10^{-07}$) for association with sporadic and familial IAs. Association with the rs1333040 SNP was also confirmed in this study,¹⁴ further strengthening association of this locus with IA.

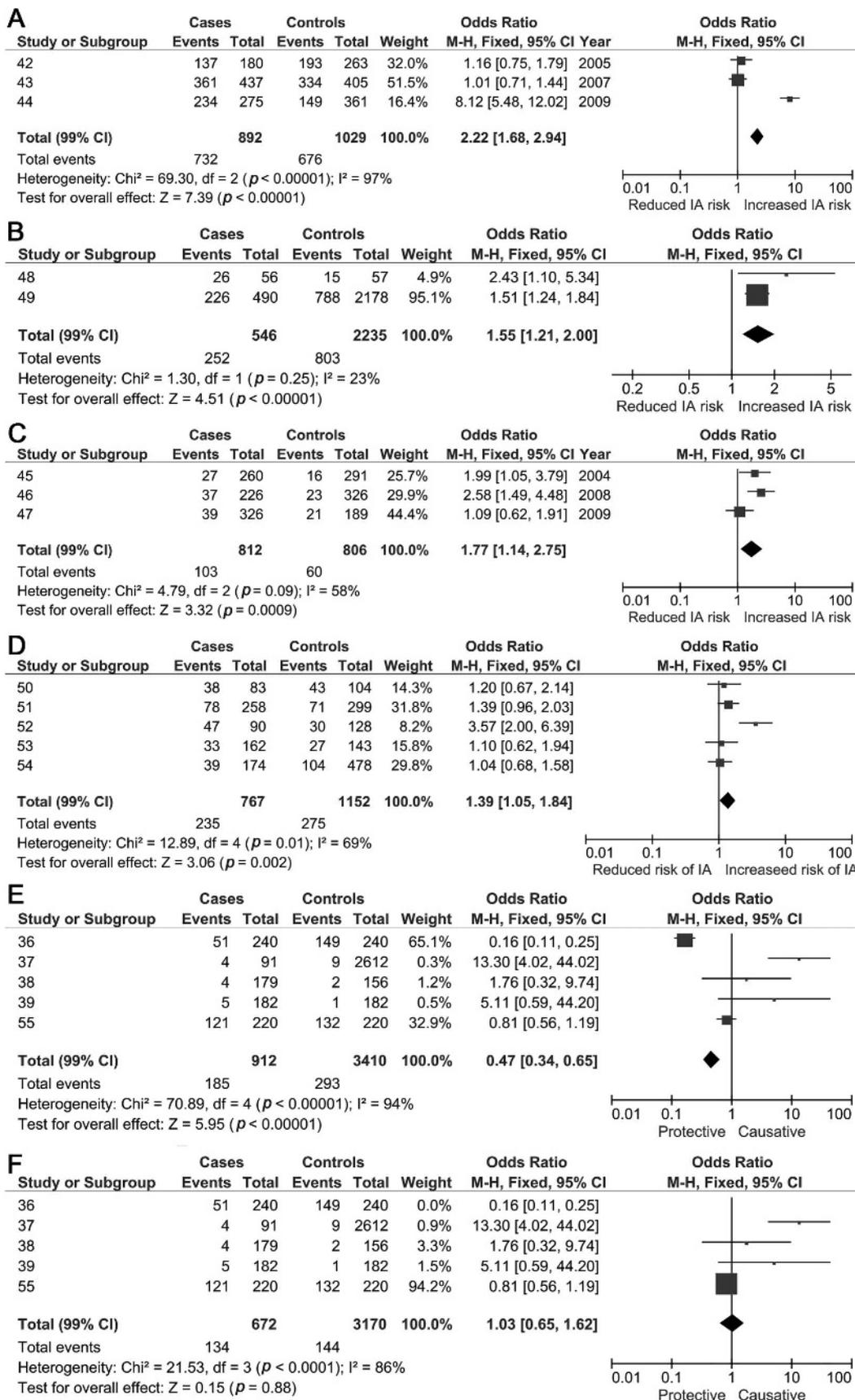
Two SNPs on chromosome 8q (rs10958409 and rs9298506), surrounding the *SOX17* gene, were studied in European and Japanese populations; rs10958409 was associated in both populations, but the rs9298506 SNP was associated with IA in the European but not Japanese population. *SOX17* plays an important role in generation and maintenance of stem cells of endothelial and hematopoietic lineages, crucial in the formation and maintenance of vascular endothelium.^{22,23} Furthermore, *SOX17* knockout mice show multiple vascular abnormalities reflecting defective endothelial remodeling.²² Defective stem cells involved in vascular maintenance are thus plausible targets in IA pathogenesis. The heterogeneity observed in the meta-analysis of these 2 SNPs may partly be explained by the difference in risk allele frequencies in the white population (table e-1)²⁴ compared with the other populations studied (rs10958409, risk allele frequency 0.88 vs approximately 0.2; rs9298506, risk allele frequency 0.17 vs approximately 0.80). Further support implicating chromosome 8 loci was shown in a recent GWAS,¹⁴ in which a novel SNP, also in the region of the *SOX17* gene, was significantly associated with IAs (rs1072737: OR 1.22; 95% CI 1.07–1.39), independent of smoking. For both *SOX17* loci, in the

Figure 2 Forest plots (additive model) for genome-wide association studies in all populations



(A) rs1333040 single nucleotide polymorphism (SNP); (B) rs10757278 SNP; (C) rs9298506; (D) rs10958409; (E) rs6841581. CI = confidence interval; IA = intracranial aneurysm.

Figure 3 Forest plots for candidate gene single nucleotide polymorphisms associated with intracranial aneurysms



(A) Dominant model forest plots for *SERPINA3* single nucleotide polymorphism (SNP). (B) *COL3A1* (rs1800255) dominant model forest plot. (C) *COL1A2* (rs42524) dominant model forest plot. (D) *ACE* I/D recessive model forest plot. (E) *IL6* G572C SNP recessive model forest plot before sensitivity analysis. (F) *IL6* G572C SNP recessive model forest plot after sensitivity analysis. CI = confidence interval; IA = intracranial aneurysm; M-H = Mantel-Haenszel.

Table 2 Random-effects and sensitivity analyses of associated SNPs that showed significant statistical heterogeneity under fixed-effects modeling

SNP	No. studies	Studies excluded	FE OR (95% CI) before adjustment	Random-effects OR (95% CI)	FE OR (95% CI) after sensitivity analysis	Genetic model
<i>SERPINA3</i>	3	Liu ⁴²	2.22 (1.68-2.94) ^a	2.12 (0.36-12.31)	1.07 (0.74-1.53)	Dominant
			1.27 (1.07-1.50) ^a	1.25 (0.61-2.59)	0.97 (0.79-1.19)	Additive
<i>ACE I/D</i>	5	Slowik ⁵⁰	1.39 (1.05-1.84) ^a	1.44 (0.86-2.42)	1.20 (0.88-1.62)	Recessive
<i>IL6 G572C</i>	5	Sun ³⁶	0.47 (0.34-0.65) ^a	1.49 (0.24-9.27)	1.03 (0.65-1.62)	Recessive
			0.61 (0.49-0.75) ^a	0.95 (0.31-2.85)	1.04 (0.79-1.39)	Additive
rs1333040	11	Low ¹³	1.23 (1.19-1.28) ^a	1.26 (1.15-1.39) ^a	1.31 (1.26-1.37) ^a	Additive
rs700651	6	Low ¹³	1.11 (1.06-1.18) ^a	1.14 (1.03-1.25) ^a	1.19 (1.11-1.28) ^a	Additive
rs9298506	8	Low ¹³	1.21 (1.15-1.27) ^a	1.24 (1.08-1.41) ^a	1.32 (1.24-1.39) ^a	Additive
rs10958409	9	4 ^{10,11,20,24b}	1.20 (1.15-1.26) ^a	1.22 (1.1-1.34) ^a	1.23 (1.17-1.3) ^a	Additive

Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; FE = fixed-effects model; IL = interleukin; OR = odds ratio; SNP = single nucleotide polymorphism.

^aSignificant association with IA.

^bFour studies, including one white population and 3 Japanese populations, were excluded.

most recent GWAS,¹⁴ smoking was an independent risk factor, acting in a multiplicative manner (chromosome 8: rs1072737; OR 2.12; 95% CI 1.76–2.56 and chromosome 9: rs6475606; OR 2.11; 95% CI 1.77–2.52).

A further recent GWAS¹² found the SNP rs6841581A>G on chromosome 4q31.23, coding for the endothelin receptor type A (*EDNRA*) gene, was significantly associated with IA in Dutch, Finnish, and Japanese populations (OR 1.22; 95% CI 1.14–1.31;

Table 3 Subgroup ethnicity analysis

SNP	No. studies	Ethnicity	FE OR, all ethnicities (all studies)	FE OR (95% CI), ethnicity subanalysis	<i>p</i> _{corrected}	<i>p</i> _{Het} (<i>I</i> ²)	Genetic model
<i>ACE I/D</i>	4/5	White	1.39 (1.05-1.84)	1.42 (1.06-1.92) ^a	0.002	0.006 (76%)	Recessive
		Japanese		1.20 (0.56-2.57)	0.54	NA	Recessive
<i>IL6 G572C</i>	3/5	Chinese	0.30 (0.19-0.47)	0.41 (0.29-0.58) ^a	<0.00001	0.0001 (95%)	Recessive
		White		4.26 (0.92-19.7)	0.1	0.03 (78%)	Recessive
	2/5	Chinese	0.58 (0.44-0.75)	0.50 (0.39-0.64) ^a	<0.00001	<0.00001 (97%)	Additive
		White		1.38 (0.83-2.29)	0.1	0.19 (42%)	Additive
rs1333040	6/11	Japanese	1.24 (1.2-1.29)	1.15 (1.09-1.22) ^a	1.75 × 10 ⁻⁰⁶	3.06 × 10 ⁻⁰⁸ (88%)	Additive
	5/11	White		1.30 (1.24-1.36) ^a	1.91 × 10 ⁻⁰⁶	0.78 (0%)	Additive
rs10757278	5/7	White	1.29 (1.21-1.38)	1.30 (1.2-1.43) ^a	1.2 × 10 ⁻⁰⁹	0.91 (0%)	Additive
	2/7	Japanese		1.27 (1.13-1.41) ^a	2.6 × 10 ⁻⁰⁵	0.22 (33%)	Additive
rs9298506	5/8	White	1.21 (1.15-1.27)	1.35 (1.27-1.44) ^a	2.4 × 10 ⁻⁰⁴	0.52 (0%)	Additive
	3/8	Japanese		1.03 (0.95-1.12)	0.45	6.54 × 10 ⁻⁰⁴ (86%)	Additive
rs10958409	5/9	White	1.2 (1.15-1.26)	1.31 (1.23-1.39) ^a	8.2 × 10 ⁻⁰²	0.052 (62%)	Additive
	4/9	Japanese		1.09 (1.02-1.17) ^a	0.009	0.08 (55%)	Additive
rs700651	3/3	White	1.11 (1.06-1.18)	1.19 (1.09-1.29) ^a	4.82 × 10 ⁻⁰⁵	0.23 (31%)	Additive
	3/3	Japanese		1.06 (0.94-1.31)	0.08	0.02 (75%)	Additive
rs6841581	4/6	White	1.22 (1.14-1.31)	1.25 (1.13-1.38) ^a	1.21 × 10 ⁻⁰⁵	0.18 (38%)	Additive
	2/6	Japanese		1.2 (1.08-1.32) ^a	3.56 × 10 ⁻⁰⁴	0.87 (0%)	Additive
rs6538595	4/6	White	1.16 (1.10-1.23)	1.16 (1.08-1.24) ^a	2.13 × 10 ⁻⁰⁵	0.91 (0%)	Additive
	2/6	Japanese		1.17 (1.06-1.28) ^a	1.49 × 10 ⁻⁰³	0.6 (0%)	Additive

Abbreviations: ACE = angiotensin-converting enzyme; CI = confidence interval; FE = fixed-effects model; *I*² = Higgins statistic demonstrating degree of interstudy heterogeneity; IA = intracranial aneurysm; IL = interleukin; NA = not applicable; OR = odds ratio; *p*_{Het} = interstudy heterogeneity *p* value; SNP = single nucleotide polymorphism.

^aSignificant association with IA.

$p = 1.95 \times 10^{-8}$). Another GWAS¹³ in a Japanese population showed that the rs6842241 SNP, located at 4q31.22 near the *EDNRA* gene, was significantly associated with IA (OR 1.25; 95% CI 1.16–1.34; $p = 9.58 \times 10^{-09}$). *EDNRA* is a G-protein-coupled receptor for endothelins, which modulate vasoconstriction and vasodilatation after hemodynamic insult. Endothelin-1—the predominant isoform in vascular smooth-muscle cells—activates *EDNRA*. Endothelin signaling is activated at the site of vascular injury,^{12,25} causing cell proliferation; indeed, after SAH, *EDNRA* and endothelin-1 protein levels are both increased in CSF.^{26–28} Alternatively, downregulation of *EDNRA* signaling could lead to defective vascular repair, allowing aneurysms to develop after injury, a hypothesis supported by functional analysis of *EDNRA* variants showing lower transcriptional activity for the rs6841581 risk allele (G).¹³

SNPs with unknown function or not examined in more than 2 studies. Five SNPs from GWAS do not correspond to genes with any known functions relevant to IA development. Two of these SNPs (rs1429412 and rs700651), at locus 2q33, flank the *BOLL* gene (involved in germ cell development) and the phospholipase C-like 1 gene (involved in intracellular cascade reactions with abolished phospholipase C activity). Phospholipase C-like 1 lies close to the vascular endothelial growth factor receptor-2, which is involved in CNS angiogenesis and is a marker for endothelial progenitor cells. Three further SNPs on chromosome 2 were associated with familial IAs: rs11693075 (close to the histone deacetylase complex *SAP130* gene), rs1897472, and rs3769801 (both located within the phosphodiesterase-1 gene).¹⁴

One associated SNP located on chromosome 7 (rs4628172 G>T) is within the *TMEM195* gene, which encodes transmembrane proteins, possibly involved in fatty acid biosynthesis and iron binding.^{11,13} Further associated SNPs from the latest GWAS include variants on chromosome 12q22 (rs6538595, rs11112585, and rs2374513) within the *C12orf75* gene.¹⁴ The rs1132274 G>T SNP on chromosome 20p12.1 was also associated with IA.¹⁰ However, none of these SNPs yet has known clear functional relevance to IA.

Three further loci not included in this meta-analysis (because they were reported in only one study) showed significant association with IAs.¹⁰ These loci included 18q11.2 (rs11661542), 10q24.32 (rs12413409), and 13q13.2 (rs9315204), but their mechanisms of association remain unclear.

Genetic variants associated with IAs identified by CGAS.

Eight SNPs from CGAS were associated with IAs in our meta-analysis, albeit with significant statistical heterogeneity. These SNPs relate to genes with

plausible relevance to IA biology, including those important for extracellular matrix integrity, inflammatory mediators, and vascular endothelium maintenance. Extracellular matrix gene variants may predispose to IA development by weakening arterial walls. In our meta-analysis, 6 such SNPs showed significant associations with IA: *COL1A2* (rs42524), *COL3A1* (rs1800255), *SERPINA3*, versican (rs251124 and rs173686), and heparan sulfate proteoglycan 2 (rs3767137). The *COL1A2* rs42524 SNP is located on chromosome 7q22.1 close to the elastin gene—a protein component of arterial walls, previously associated with IAs in a linkage-association study.²⁹ Collagen type 1 is usually found in the adventitial layer of cerebral arteries and provides tensile strength, making it a plausible factor in IA development. Nevertheless, caution is needed in generalizing this result as all 3 studies identified were in Far East populations; for robust association to be confirmed, this SNP has to be examined in other populations, including Europe, because risk allele frequencies may differ. Collagen type 3 (*COL3A1*) was investigated in 3 Chinese populations; rs1800255 (G>A) was the only SNP significantly associated with IA, but replication in other ethnicities and larger cohorts is required to confirm these findings.

We also found associations between 2 versican genetic variants (rs251124 and rs173686) and IAs in Dutch, Japanese, and Chinese populations.^{30–32} In a previous linkage study on a Japanese cohort, chromosome 5q14.3, very close to the versican gene, was implicated in IA.³⁰ In vivo studies on abdominal aortic aneurysm samples found reduced versican messenger RNA expression,^{33,34} which could reflect a decline in smooth-muscle cells associated with weakness in the vascular wall. Moreover, a GWAS³⁵ on thoracic and aortic dissections showed significant association with the 5q13–14 locus, corresponding to the versican gene.

The proinflammatory cytokine *IL6* G572C SNP had an overall protective association with IAs in a recessive model. However, there was significant statistical heterogeneity, and sensitivity analysis revealed no association once one Chinese study³⁶ was excluded, which may partly reflect the greater risk allele frequency (0.79 vs 0.05–0.09) and inclusion of only unruptured IAs in this study.³⁶ Another source of heterogeneity may be sex, because one other study³⁷ included only male controls, and this may not be appropriate because SAH has a female predominance. Therefore, the overall association of this SNP with IA is not robust. Sustained abnormal vascular remodeling in association with inflammation is hypothesized to be a key mechanism in IA development.²² IL-6 can injure vessel walls by inhibiting collagen synthesis, thus increasing wall fragility and increasing the risk of aneurysmal dilatation. IL-6 levels are increased in the CSF and plasma after

SAH,^{38,39} but whether this is directly related to the G572C SNP remains uncertain because in these studies patients were not genotyped for the mutant allele; moreover, IL-6 may be released as part of a systemic inflammatory response in the acute phase after SAH.

Strengths of our study. Our systematic review and meta-analysis is the largest and most comprehensive to date on genetic variants associated with IAs. We assessed strength of association by using multiple genetic models and carefully assessed the robustness of all associations by performing random-effects, sensitivity, and ethnic subgroup analyses. We conducted our analysis and reporting according to quality guidelines for genetic association studies, including Human Genome Epidemiology Network¹⁵ and Strengthening the Reporting of Genetic Association Studies.¹⁷

Limitations of our study. Our assessment of interstudy heterogeneity by visual inspection of the forest plots and sensitivity analyses only partly addresses potential sources of heterogeneity between studies. Further individual patient data are required on other factors that could also contribute to heterogeneity, such as sex proportions, age, genotyping methods or errors, disease phenotype (aneurysm size, location, and rupture status), and environmental risk factor status. Our meta-analysis was only able to pool reported positively associated SNPs from the 6 GWAS studies, but data on many SNPs sequenced not reaching the threshold for GWAS statistical significance were not available, thus limiting our meta-analysis to 41 SNPs in total. Indeed, for many of the candidate-gene studies, pooling all available data from GWAS might allow more robust risk estimates to be calculated; despite 8 candidate gene SNPs being associated with IAs, on average only 2.7 publications were available for each variant.

We have identified 19 candidate SNPs associated with IAs, of which 16 were robust to random-effects or sensitivity analyses. The ORs suggest that the genetic contribution to aneurysm development is substantial, but the variants identified implicate multiple pathophysiologic mechanisms, particularly involving vascular endothelium maintenance. Nevertheless, the amount of data on genetic associations with IAs remains much smaller than for other complex diseases, so further large replication studies in a full spectrum of populations are required, ideally using GWAS or exome sequencing to identify rarer functional variants. A limitation of most studies included is that both ruptured and unruptured IAs were analyzed together; because only a minority of IAs are destined to rupture, future studies should address genetic risk factors specifically related to rupture status. Another important area for future research is to explore how genetic factors are related to

aneurysm location, size, or morphology, because there may be specific genetic associations for particular aneurysm phenotypes (which may also relate to rupture risk). Finally, validation studies of risk models in prospective cohorts (e.g., of unruptured IAs followed up for rupture risk) would be helpful in determining the relevance of genetic risk loci in addition to well-established risk factors for overall disease phenotype, to ultimately reduce the devastating burden of aneurysmal SAH.

AUTHOR CONTRIBUTIONS

Dr. Alg designed the study, performed the literature search, acquired and carried out the statistical analysis of the data, and drafted the manuscript. Dr. Sofat analyzed and interpreted the data and revised the manuscript. Dr. Houlden supervised the study, analyzed and interpreted the data, and provided revisions to the manuscript. Dr. Werring conceived and supervised the study, checked the literature search, interpreted the results, and provided critical revisions to the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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