

Genetic basis of intracranial aneurysm formation and rupture: clinical implications in the postgenomic era

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OBJECTIVE Despite the prevalence and impact of intracranial aneurysms (IAs), the molecular basis of their pathogenesis remains largely unknown. Moreover, there is a dearth of clinically validated biomarkers to efficiently screen patients with IAs and prognosticate risk for rupture. The aim of this study was to survey the literature to systematically identify the spectrum of genetic aberrations that have been identified in IA formation and risk of rupture.

METHODS A literature search was performed using the Medical Subject Headings (MeSH) system of databases including PubMed, EMBASE, and Google Scholar. Relevant studies that reported on genetic analyses of IAs, rupture risk, and long-term outcomes were included in the qualitative analysis.

RESULTS A total of 114 studies were reviewed and 65 were included in the qualitative synthesis. There are several well-established mendelian syndromes that confer risk to IAs, with variable frequency. Linkage analyses, genome-wide association studies, candidate gene studies, and exome sequencing identify several recurrent polymorphic variants at candidate loci, and genes associated with the risk of aneurysm formation and rupture, including *ANRIL* (*CDKN2B-AS1*, 9p21), *ARGHEF17* (11q13), *ELN* (7q11), *SERPINA3* (14q32), and *SOX17* (8q11). In addition, polymorphisms in *eNOS*/*NOS3* (7q36) may serve as predictive markers for outcomes following intracranial aneurysm rupture. Genetic aberrations identified to date converge on posited molecular mechanisms involved in vascular remodeling, with strong implications for an associated immune-mediated inflammatory response.

CONCLUSIONS Comprehensive studies of IA formation and rupture have identified candidate risk variants and loci; however, further genome-wide analyses are needed to identify high-confidence genetic aberrations. The literature supports a role for several risk loci in aneurysm formation and rupture with putative candidate genes. A thorough understanding of the genetic basis governing risk of IA development and the resultant aneurysmal subarachnoid hemorrhage may aid in screening, clinical management, and risk stratification of these patients, and it may also enable identification of putative mechanisms for future drug development.

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KEYWORDS intracranial aneurysm; gene; genetic; risk; polymorphism

INTRACRANIAL aneurysms (IAs) are pathological dilations of cerebral vasculature, most commonly occurring at bifurcations of major intracranial arteries, and are estimated to occur in up to 6% of adults worldwide.⁵⁴ Approximately 2% of these aneurysms ultimately rupture, as inferred from the cumulative incidence of aneurysmal subarachnoid hemorrhage (aSAH).⁵⁴ Unruptured aneurysms may be detected incidentally through cranial imaging for trauma or alternate pathologies, or through deliberate screening of high-risk individuals, such as those with a

family history of IAs. The most devastating consequence of IA rupture is aSAH, with an impact ranging from mild symptoms to severe disability or mortality. The mortality rate associated with aSAH is estimated to be approximately one-third to one-half of patients, and this figure has remained relatively unchanged in the past several decades.⁵¹ The management of unruptured IAs has been the source of intensive study and debate, and requires meticulous consideration of the risk of rupture along with the perioperative risks of intervention.²²

ABBREVIATIONS ADPKD = autosomal dominant polycystic kidney disease; aSAH = aneurysmal subarachnoid hemorrhage; DCI = delayed cerebral ischemia; EDS = Ehlers-Danlos syndrome; eNOS = endothelial nitric oxide synthase; GWAS = genome-wide association studies; IAs = intracranial aneurysms; LDS = Loeys-Dietz syndrome; MMPs = matrix metalloproteinases; NF1 = neurofibromatosis type 1; TSC = tuberous sclerosis complex; WES = whole-exome sequencing.

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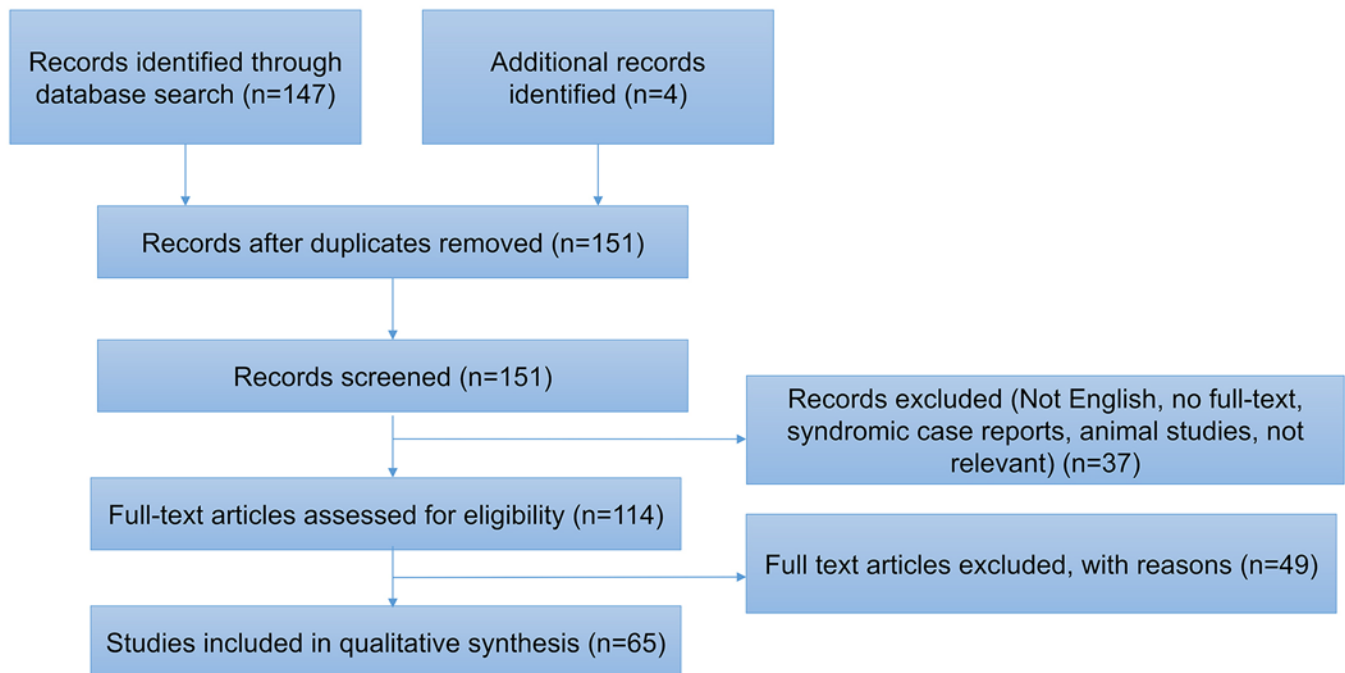


FIG. 1. PRISMA-style flowchart for record screening and inclusion for review.

However, despite the prevalence and impact of IAs, their pathogenesis remains largely unknown. In addition, although the management of patients with both ruptured and unruptured IAs is highly nuanced, clinical decision-making in this patient population has not involved prognostic markers. Intensive clinical research has been undertaken to better define the natural history of unruptured IAs, yet screening for IAs to assess risk of aSAH has not been implemented because biomarkers have not been clinically validated. Similarly, although the risk of rupture of IAs has been widely studied and is dependent on several aneurysm-related and patient-specific variables, genetic interactions with these variables have not yet been validated.

A heritable contribution to aneurysm formation and rupture is estimated to be present in up to 40% of cases, with the remaining cases probably attributable to gene–environment interactions that lead to sporadic IA formation.³⁵ Familial clustering of IAs in the general population, as well as the association with mendelian disorders in IAs provide strong evidence for genetic underpinnings of this disease.⁵⁸ Meta-analyses of studies in the literature support the theory that IAs are caused by significant genetic heterogeneity and polygenic contributions to the risk of formation and rupture.⁵⁷ Moreover, studies have shown that there is an approximately 17 times greater risk of aneurysm rupture in familial IAs as compared with sporadic IAs, when matched for size and location.¹³ Much like other areas of medicine, including oncology, where thorough genetic analyses have enabled identification of clinically relevant subtypes, there is evidence for a genetic basis in subpopulations of aneurysms that are more prone to rupture than others, depending on their size and history of formation.³⁰

In order to continue to advance the field of vascular neurosurgery, new therapies informed by the mechanisms of disease are imperative. An understanding of the genetics and mechanisms governing IA pathophysiology can therefore guide future treatment and management of this challenging clinical entity. Mechanisms involving inflammatory responses and vascular remodeling have been proposed to comprise the basis of genetic dysregulation, and familial studies have provided support in this regard. Accordingly, this report details a review of genetic studies on IAs in the literature, highlights putative disease-related genes and posited mechanisms, and discusses the implications for clinical applications.

Methods

A literature search was performed using the Medical Subject Headings (MeSH) system of databases including PubMed, EMBASE, and Google Scholar. There were no date restrictions imposed. All articles that were included contained the terms “Intracranial aneurysm” OR “brain aneurysm” AND “gene” OR “genetic” OR “SNPs” [single nucleotide polymorphisms]. A PRISMA-style flowchart of the search findings is detailed in Fig. 1. One hundred forty-seven articles were identified from this initial screen and another 4 articles were obtained from a survey of other databases using the same search terms. There were no instances of duplicate studies. Of the 151 records screened, 49 were excluded. Only English articles were included, and reports on animals or animal models (37 articles) were not included in the final list of studies.

In accordance with the Cochrane Risk of Bias Tool, study bias risk was assessed. Selection bias was addressed by including studies based on the criteria outlined: studies

TABLE 1. Literature review of autosomal dominant mendelian syndromes associated with risk of IAs

Authors & Year	Gene	Associated Syndrome	Known Implications & Disease Prevalence
Kim et al., 2016 Schievink et al., 1994	<i>COL3A1</i>	Vascular EDS (type IV)	IAs have been reported in both classic & nonclassic forms of EDS; patients w/ vascular subtype of EDS are at highest risk for IA formation (12%).
Conway et al., 2001 Kim et al., 2016	<i>FBN1</i>	Marfan syndrome	Study results are conflicting regarding estimate of prevalence. Earlier reports failed to identify an association btwn IAs & Marfan syndrome on autopsy; estimated prevalence of at least 1 aneurysm is ~ 14%.
Rossetti & Harris, 2013	<i>PKD1</i> <i>PKD2</i>	ADPKD	Prevalence of 12.4% of IAs in general ADPKD population, w/ an age-dependent increase of prevalence, w/ a peak of 23.3% in patients older than 60 yrs. Risk is strongly associated w/ family history of rupture. The estimated prevalence of uIAs in patients w/ ADPKD w/ a family history of IAs &/or SAH is 21.2%, whereas the estimated prevalence of uIAs in ADPKD patients w/o such a history is 6.3%.
Kim et al., 2016 Loeys et al., 2006 Rodrigues et al., 2009	<i>SMAD3</i> <i>TGFBR1</i> <i>TGFBR2</i>	LDS	Intracranial bleeding secondary to vascular pathology is the 3rd leading cause of death in patients w/ LDS; prevalence of IAs estimated to range btwn 10% & 28%.

uIAs = unruptured IAs.

reporting on genetic analyses were included and those on expression alone were omitted. Systematic reviews, familial studies, clinical case series, whole-exome sequencing (WES), whole transcriptome sequencing, genome-wide association studies (GWAS), and candidate gene studies were all included. Reviews were also included in the qualitative analysis. Case reports of IAs arising in the context of rare syndromic clinical entities were excluded. One study reporting on genetic risk of de novo aneurysm formation secondary to an iatrogenic complication was also excluded. A total of 65 articles met sufficient criteria to be included in the qualitative analysis. The most recent MeSH search was performed on February 15, 2019. Polymorphic variants were tabulated if statistical significance reached a p value less than 1.0×10^{-6} . For candidate gene studies, a minimum of 500 combined samples derived from cases and controls was used for the genes to be tabulated, a cutoff consistent with other reviews and meta-analyses in the literature. Candidate variants that reached borderline statistical significance were not included. There were no sample size restrictions for whole-exome- or whole-genome-based studies.

Results

Genetic Aberrations Identified Through Familial and Genome-Directed Studies

Aneurysm Formation: Known Genes Associated With Mendelian Syndromes

There are numerous well-recognized mendelian disorders that confer an increased risk of developing IAs. Over the past few decades, there has been reconsideration of the concept of single gene mutations causing single clinical phenotypes and instead, a paradigm shift toward conceptualization of interactions between single gene mendelian phenotypes and allelic variants at other chromosomal loci, or so-called transacting regulatory elements. As a result, traditional mendelian views of disease inheritance have shifted from dichotomous disease states toward a continuous spectrum.⁴⁹ The etiology of this variability remains

unclear; however, the high degree of pleiotropy of IA formation within and across genetic syndromes is clinically evident.

Approaches to identifying IA-related genes include linkage analysis in large families and candidate gene approaches.⁷⁰ Familial studies have largely focused on candidate genes that play a role in maintenance and repair of the arterial wall (Table 1).⁵⁹ Perhaps one of the most well-characterized mendelian syndromes conferring an increased risk to IAs is autosomal dominant polycystic kidney disease (ADPKD), and in fact this disease imparts the highest risk of IAs among the other mendelian syndromes associated with a higher risk of IA formation than the general population.⁵⁰ ADPKD is caused by mutations in *PKD1* in 85% of cases and by *PKD2* mutations in the remaining 15%. The renal-specific disease spectrum of ADPKD is highly variable, as is the risk of IAs. IAs are the most life-threatening feature of this syndrome and have an estimated prevalence of 12.4%, with a peak prevalence of 23.3% in patients older than 60 years of age.⁵⁶ In some instances, devastating SAH may be the first presentation in a patient with ADPKD, as in other mendelian syndromes.^{5,29} Screening for IAs is typically recommended in patients with known ADPKD who are older than 30 years, and in normotensive individuals in this patient population.⁶⁶ Of note, the *PKD1* gene resides at 16p13, the same locus harboring the *TSC2* gene, in which mutations are associated with tuberous sclerosis complex (TSC). Contiguous genetic aberrations encompassing these genes, such as deletions, have been identified, which thereby lead to a concurrent syndrome of ADPKD and TSC.^{16,46} This rare subset of patients is at a much higher risk of developing IAs, demonstrating the impact of modifier genes on mendelian phenotypes.

IAs have been described in a number of mendelian connective tissue disorders, including vascular Ehlers-Danlos syndrome (EDS, formerly referred to as Ehlers-Danlos type IV) associated with mutations in *COL3A1*; Loeys-Dietz syndrome (LDS) associated with pathogenic mutations in genes involved in the transforming growth factor β (TGF β) pathway; and Marfan syndrome associ-

ated with mutations in *FBNI*³³ (Table 1). As outlined in greater detail below, the pathological mechanisms underlying this susceptibility are probably related to structural vulnerabilities in the intracranial vasculature as a result of malfunction of the respective genes. With regard to EDS, consensus guidelines for screening are lacking, and are often considered on a patient-specific basis. LDS is characterized by severe vascular defects predominantly affecting the arterial system, with a high risk of aneurysmal arterial hemorrhage or dissection at a young age.⁴⁴ Intracranial bleeding secondary to vascular pathology is the third leading cause of death in patients with LDS, with a prevalence of IAs estimated to range between 10% and 28%.^{33,45,55} In Marfan syndrome, aortic aneurysms and dissections are the most commonly associated vascular pathologies, and multiple reports suggest an association with IAs. Other syndromes outside of the classic connective tissue disorders are also associated with IAs in lower frequency, including neurofibromatosis type 1 (NF1). In addition to the well-characterized constellation of clinical criteria for NF1, IAs have been reported in up to 11% of patients; however, studies on prevalence are conflicting.¹⁸ Other studies have suggested an association between autosomal dominant mendelian disorders such as hereditary hemorrhagic telangiectasia, but have failed to demonstrate a prevalence of aneurysms that is higher than in the general population.¹²

Last, there are syndromes inherited in an autosomal recessive fashion or that arise from de novo genetic changes that have also been shown to be associated with IAs, although in lower frequency than the syndromes listed above. These include patients with pseudoxanthoma elasticum, which is associated with mutations in the *ABCC6* gene on chromosome 16p13. It has been posited that IAs in this syndrome may form as a result of abnormal elastic lamina in the intracranial vasculature, predominantly in the intracranial internal carotid artery.^{11,48} Finally, emerging evidence through WES suggests a role for the *PCNT* gene in cerebrovascular disease. This gene encodes a protein involved in microtubule nucleation and organization in the cell cycle, and biallelic loss-of-function mutations are known to cause microcephalic osteodysplastic primordial dwarfism type II. In more than half of cases, patients with point mutations in *PCNT* are thought to develop IAs, and this genetic aberration may also confer a risk of developing multiple IAs in the same individual.⁴² Although these genetic aberrations provide clues to the basis of aneurysm formation, the risks associated with rupture in these individual syndromes remains to be determined.

Polymorphic Variants and Respective Susceptibility Loci

Identification of genetic variants contributing to the risk of formation and rupture of IAs beyond well-characterized mendelian syndromes has occurred largely through linkage analyses, GWAS to identify risk loci, candidate gene approaches and, more recently, whole-exome-based analyses. GWAS have served as the principal methodology for identifying genetic factors associated with IAs and have identified several risk loci and associated candidate genes in various ethnic patient cohorts, such as European, Finnish, Japanese, and French-Canadian populations. Risk

loci and candidate genes include the following: 4q31.22 (*EDNRA*), 8q11.23 (*SOX17*), 7p21.1 (*HDAC9*), 9p21.3–23.1 (*CDKN2A-CDKN2BAS*), 11q13 (*ARHGEF17*), 13q13.1 (*STARD13-KL*), and 18q11.2 (*RBBP8*) (Table 2, $p < 1.0 \times 10^{-6}$).^{1,2,10,17,19,20,37,38,43,47,65,68,69} Many of these regions also overlap with population-based studies of Kazakh patients in smaller cohorts, which may be insufficient for genome-wide discovery but useful for candidate-gene-based validation.⁷² A large locus encompassing numerous candidate genes on chromosome 19q13 has also been implicated.⁶² Further studies of French-Canadian families have identified additional novel genes and loci including *FHIT* (3p14, rs1554600, $p = 4 \times 10^{-9}$) and *CCDC80* (rs78125721, $p = 4.77 \times 10^{-7}$),⁷⁴ as well as the 8p23.1 and 18q11.2 loci.

Additional polymorphic variants have been identified both in the above-mentioned studies and in others, although with a lower level of statistical significance. Accordingly, the expected role of these variants in the development of IAs is less robust, or may be more significant in the context of other regulatory variants. This includes other polymorphic variants in the aforementioned genes, including *CDKN2BAS* and *SOX17*, which are both recurrently implicated in IA formation across multiple studies.¹⁵ The first WES study of IAs examined 12 Japanese families, and only one variant in *ADAMTS15* (rs185269810) reached a statistically significant association in both the initial and validation cohorts.⁶⁷ Further supporting a role for *ADAMTS* genes, recent case-control studies and meta-analyses have further implicated polymorphisms in genes encoding matrix metalloproteases (MMPs) such as *ADAMTS2* (rs11750568: OR 1.32, $p = 0.006$), as well as other *ADAMTS* family genes (*ADAMTS12* variant rs1364044: OR 0.65, $p = 0.0001$; *ADAMTS13* variants rs739469 and rs4962153: OR 0.77 and 0.63, $p = 0.02$ and 0.0006, respectively).^{3,8} Of the WES studies in the literature, there was no overlap between the variants in the implicated genes.^{67,73,76}

It is important to note that numerous studies identify risk loci alone and require further functional validation in order to narrow the number of candidate causative genes at the respective chromosomal locus. However, there are implications for modifier alleles playing a role in intergenic regions that harbor regulatory elements.³⁹

Genetic Modifiers of Aneurysm Rupture and Subsequent Outcomes

In addition to genetic variants underlying the presence or formation of IAs, there are rich data that can be mined to identify risk loci for aneurysmal rupture and clinical outcomes following aSAH. Following rupture, the genetics of this disease are further complicated by etiologies that may govern other dimensions of SAH care, including vasospasm, which has been regarded as a principal cause of devastating outcomes related to delayed cerebral ischemia (DCI). There is a dearth of studies reporting on this outcome and, of the few that exist in the literature, many are not sufficiently powered to draw robust conclusions. Studies of outcomes primarily report on gene expression profiles, which are inherently dynamic, rather than static genetic aberrations that may define a static measure of risk.^{9,63}

TABLE 2. Literature review of polymorphic variants implicated in susceptibility of formation and rupture of IAs

Authors & Year	Gene	Locus	Variant Allele	OR [95% CI]
Chen et al., 2013	<i>ACE</i>	17q23.3	rs4646994	1.27 [1.03–1.57]
Kurki et al., 2014	<i>ANKRD44</i>	2q33	rs919433	1.25 (not reported)
			rs12472355	1.24 (not reported)
Alg et al., 2013	<i>ANRIL (CDKN2B-AS1)</i>	9p21	rs1333040	1.24 [1.2–1.29]
			rs10757278	1.29 [1.21–1.38]
Foroud et al., 2012			rs6475606	1.35 (not reported)
Foroud et al., 2014			rs10733376	1.34 [1.231.45]
Kurki et al., 2014			rs1333042	1.32 (not reported)
Yang et al., 2018	<i>ARHGEF17</i>	11q13	rs2298808	6.6 [2.9–15.8]
Yasuno et al., 2010	<i>CNNM2</i>	10q24	rs124123409	1.29 [1.19–1.40]
Alg et al., 2013	<i>COL1A2</i>	7q21	rs42524	1.77 [1.14–2.75]
	<i>COL1A3</i>	2q32	rs1080255	1.55 [1.21–2.00]
	<i>EDNRA</i>	4q31	rs6841581	1.22 [1.14–1.31]
Akagawa et al., 2006	<i>ELN</i>	7q11	rs8326	3.11 [1.96–5.45]
Lin et al., 2014	<i>ENG</i>	9q34	rs1800956	1.56 [1.08–2.26]
Kurki et al., 2014	<i>EPM2A</i>	6q24	rs75018213	2.11 (not reported)
Alg et al., 2013	<i>FGD6</i>	12q22	rs6538595	1.16 [1.10–1.23]
Kurki et al., 2014	<i>FSTL4</i>	5q31	rs113816216	2.31 (not reported)
Foroud et al., 2014	<i>HDAC9</i>	7p21	rs10230207	1.27 [1.17–1.38]
Alg et al., 2013	<i>HSPG2</i>	1p36	rs3767137	1.22 [1.08–1.39]
	<i>IL6</i>	7p15	rs1800796	0.47 [0.34–0.65]
Krischek et al., 2010	<i>JDP2</i>	14q24	rs175646	1.44 [1.15–1.81]
Weinsheimer et al., 2007	<i>KLK8</i>	19q13	rs1722561	1.35 [1.14–1.60]
Low et al., 2011	<i>LIMK1</i>	7q11	rs6460071	1.31 [1.12–1.53]
Kurki et al., 2014	<i>LYPD6</i>	2q23	rs74972714	2.73 (not reported)
Foroud et al., 2012	<i>PDE1A</i>	2q33	rs1897472	1.78 (not reported)
			rs3769801	1.79 (not reported)
Bilguvar et al., 2008	<i>PLCL1</i>	2q32	rs700675	1.22 [1.13–1.32]
Yasuno et al., 2010	<i>RBBP8</i>	18q11	rs11661542	1.21 [1.14–1.30]
Alg et al., 2013	<i>RRBP1</i>	20p12	rs11332274	1.19 [1.11–1.28]
	<i>SERPINA3</i>	14q32	rs4934	2.22 [1.68–2.94]
	<i>SOX17</i>	8q11	rs10958409	1.20 [1.15–1.26]
			rs9298506	1.21 [1.15–1.27]
Bilguvar et al., 2008	<i>STARD13</i>	13q13	rs9135204	1.20 [1.13–1.28]

Complementary studies of variants have also identified the presence of aneurysms as well as subsets of patients with aneurysms that are more likely to rupture, including tandem repeats in endothelial nitric oxide synthase (*eNOS/NOS3*) polymorphisms, with an OR as high as 11.4 (95% CI 1.7–75.9, $p = 0.004$) for individuals harboring 3 distinct variant alleles in this gene.^{30,31,52} Further studies of *eNOS* polymorphic variants have suggested an association between rs2070744 and DCI following aSAH; however, these results only reached borderline significance (OR 2.936, 95% CI 1.048–8.226; $p = 0.040$).²⁴ Data from the same group also implicates a variant in *HMGB1* in DCI (rs2249825: OR 5.695, 95% CI 1.804–17.975; $p = 0.003$).²⁵ Finally, there has been intensive investigation of *APOE* variants in candidate-gene-based studies and their impact on functional outcome in SAH. These studies have yielded

mixed findings, with some reporting minor implications and others reporting no statistically significant associations.^{21,26,28,40,60}

Posited Mechanisms of Aneurysm Formation and Rupture Risk: Vascular Remodeling and Inflammation

The syndromic disorder most strongly associated with IAs is ADPKD.⁵⁶ Both genes implicated in this disease, *PKD1* and *PKD2*, are expressed in the smooth-muscle cells of the tunica media and myofibroblasts in blood vessels.^{23,61} Similarly, the role of collagen genes and genes in the TGF β pathway in vascular remodeling is well established, although the exact mechanisms remain unclear.⁵⁶ Of the aforementioned genetic variants that are highly statistically significant in polymorphisms identified through

GWAS, the unifying theme of these genes is their role in vascular remodeling and endothelial maintenance.⁴ For example, *SOX17* is required for both endothelial formation and maintenance, whereas other genes such as *CDKN2B* and *ANRIL* (noncoding), and *STARD13* function in cell cycle regulation and progression.^{27,32,41,64} Accordingly, these genes may govern a balance in cell cycle regulation in the arterial wall. Similarly, MMP variants such as in the *ADAMTS* gene family also suggest that defects in these genes may compromise endothelial wall integrity and, coupled with inflammatory processes, may trigger vascular remodeling along the pathway of IA formation.⁸ The protein products of these genes are known to localize to dense plaques of intracranial arteries, which strongly supports their role in the development and maintenance of myoelastic arterial walls.⁵⁶

Many of the identifying gene candidates are also involved in the inflammatory cascade, including MMPs, TGF β proteins, and eNOS.¹⁴ Functionally, there is strong evidence to support a role for inflammatory reactions with aneurysm formation. In particular, an inflammatory response is triggered by endothelial dysfunction and compromised cell wall integrity.¹⁴ Such a model is supported whereby recruitment of inflammatory mediators to the cell wall disrupts the internal elastic lamina, initiating the formation process. Further damage to the cell wall resulting in cell death and degeneration ultimately predisposes to rupture. Similarly, mounting evidence suggests a role for NF- κ B as a critical mediator of cerebral aneurysm formation through its role in the inflammatory response in which macrophage recruitment and activation occur.^{6,7,53} Further supporting a role for the immune response in IA pathology and rupture risk, RNA sequencing studies have identified the lysosomal pathway and immunoglobulins in this context.³⁴

Discussion

This systematic review was aimed at comprehensively assessing and appraising the literature pertaining to the genetics of aneurysm formation and rupture risk. It is evident that there is significant heterogeneity with regard to the quality of studies, and among the rigorously designed studies, many report borderline statistical significance of candidate loci. Moreover, the literature is variable with regard to studies on this topic, and most pertain to the presence of IAs rather than genetic predictors of rupture and outcome risk. In the presence of known risk factors for rupture, genetic variables do not yet integrate into these algorithms.²² Similarly, there is also a lack of studies reporting on the association between aneurysmal rupture and gene–environment interactions. The natural history of IAs has been intensively studied, and modifiers of natural history in the context of genetic changes probably exist but remain to be discovered. Because these are polygenic traits, there is probably also some contribution of genetic predisposition in the presence of known risk factors for formation and rupture. Moreover, an important consideration is that there may exist genetic risk factors for IAs that overlap with other intracranial vascular lesions such as arteriovenous malformations. Arteriovenous malformations often have

associated prenatal aneurysms, suggesting there may be a common basis to the pathophysiology of their formation. Meta-analyses have implicated *SOX17* in this regard, and this is a highly recurrent gene in IA studies.³⁶

The findings from this study highlight several important considerations, as well as implications for screening and future studies. Well-known syndromes associated with IAs are thought to arise secondary to dysfunction in genes that play a critical regulatory role in vessel formation. This is mirrored in the genes identified in GWAS and candidate gene analyses. There remains an important gap between the genetic risk of aneurysm formation and predictors of outcomes. Common converging themes include vascular remodeling and an associated inflammatory response. This may suggest an important role for immune-modifying medications in patients at high risk for aneurysm rupture on the basis of established clinical paradigms.²²

Some study limitations should be noted. This study was limited in that only English-language studies were included, and may have missed other potentially significant variants in the non-English literature. Moreover, the study was restricted to reports on genetic changes, which may only represent the tip of the iceberg in our understanding of the molecular basis of IAs. As in other complex multi-genetic conditions, such as autoimmune disease or cancer, there may be a prominent role for epigenetic changes governing the pathophysiology of vasculature remodeling and IA formation risk.^{71,75} In addition, although this study was oriented toward identifying putative genes in risk loci, it is possible that modifier alleles in intergenic regions may harbor regulatory elements that are of functional significance.³⁹ Finally, our study specifically did not encompass analyses of gene expression. The extent to which variability in gene expression contributes to aneurysm risk is still unclear, but may provide some clues regarding underlying genetic dysfunction.

Conclusions

There is a sizeable body of literature implicating genetic mutations and polymorphisms in the pathogenesis of IAs, with a varying degree of quality. There are probably germline variants of differential penetrance that contribute to risk, and the extent of polygenic interactions remains to be determined. Several candidate genes warrant further investigation, and assessment of the clinical implications of the rationale for use of immune-modifying agents may be rooted in the genetics governing IAs. Future studies should be aimed at unbiased and genome-wide analyses investigating the role of new genes in aneurysm formation and rupture, and may provide important clues for putative biomarkers. Moving forward, development of prediction models that incorporate well-validated genetic changes are needed. With the currently available tools in this post-genomic era, genome-wide analyses of large cohorts of patients with IA is the direction that is necessary to further our understanding of the genetics of this complex disease entity.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: both authors. Acquisition of data: Samuel. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Radovanovic. Statistical analysis: both authors. Administrative/technical/material support: Radovanovic. Study supervision: both authors.

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