Genome-Wide Association Studies of Intracranial Aneurysms
An Update

Ibrahim Hussain, MD; Ennis Jesus Duffis, MD; Chirag D. Gandhi, MD; Charles J. Prestigiacomo, MD

Intracranial aneurysms (IAs) affect 2% to 5% of the population and can have catastrophic results on rupture, accounting for 80% all of subarachnoid hemorrhages (SAHs).1–4 This medical and surgical emergency carries a 40% to 50% mortality rate, with 12% of individuals expiring before receiving any medical attention.5 Survivorship is fraught with socioeconomic challenges because two thirds of patients are left with some form of permanent neurological deficit.4 Although most IAs do not cause clinical symptoms during life,6,7 the substantial mortality rate with initial presentation underscores the importance of early diagnosis and intervention in high-risk groups. Advances in neuroimaging, microsurgical clipping, and minimally invasive endovascular modalities have helped reduce the burden of these morbid events; however, patient selection remains controversial given the unpredictable nature of aneurysm progression. Likewise, appropriate management is confounded by complex influences from environmental and genetic factors.

Individuals aged 40 to 60 years are at highest risk for IAs, with women affected more than men by a 3:2 ratio.7,8 Other modifiable risk factors are hypertension, atherosclerosis, smoking, and alcohol consumption.9,10 In addition to aneurysm size and location within the cerebrovasculature, these factors are used clinically to assess rupture risk.7 Certain inherited syndromes predispose individuals to the formation of IAs, including Autosomal Dominant Polycystic Kidney Disease and Ehlers–Danlos syndrome.11–13 Although individuals with these syndromes should be screened with computed tomography or magnetic resonance angiography when there is family history of stroke or SAH, they account for only 10% of all cases.14 In the absence of known predisposing genetic mutations, individuals with first-degree relatives with IAs are 4x more likely to develop IAs themselves.15 Moreover, evidence shows that these aneurysms present earlier in life and rupture at smaller sizes compared with those that develop sporadically in individuals with no family history of cerebrovascular events.16 Although genome-wide linkage studies of nonsyndromic, familial IAs have shed light on susceptibility loci and often associated with sporadic and familial IAs independent of exogenous risk factors. Subsequent studies using expanded population cohorts have now conclusively demonstrated alterations in previously unrecognized genes regulating angiogenesis, vasculogenesis, stem cell differentiation, and cell cycle progression. Although only 4 GWAS to date have analyzed enough participants (>3000 cases and controls) to identify SNPs associated with IAs at genomically significant thresholds (P value ≤1×10-7), future large-scale analyses will be powered to discover rarer risk loci and implicated genes. Furthermore, a more comprehensive understanding of independent and interdependent molecular pathways germane to IA formation and rupture may guide physicians 1 day in developing targeted therapies and optimizing prognostic risk assessment. In this review, the authors present the most up-to-date findings from GWAS of IAs, and discuss the implications of these discoveries for future diagnostic and therapeutic management.

Previous Candidate Gene Studies

Before the introduction of GWAS, global gene expression and genome-wide linkage analyses were the primary vehicles for investigating genotype-phenotype associations for IAs. Gene expression studies using microarrays to catalog the transcriptome of sporadic IAs have been ongoing since 2001,23–28 demonstrating abnormal transcription in proteins germane to collagens, matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, and cell adhesion molecules.24,25,28–30 Among other candidate genes described in the extrapolation of results to the general population. Genome-wide association studies (GWAS) provide an alternative approach to elucidate the influence of genetic variants in complex, multifactorial disorders. GWAS of other vascular diseases, including hypertension29 and ischemic stroke,30 have already yielded insight into previously unknown genes which may aid in future management and therapy. In this regard, a large-scale GWA study of IAs was first published in 2008 through the pioneering work of Günel et al,22 which helped identify a number of single-nucleotide polymorphisms (SNPs) in loci that were associated with sporadic and familial IAs independent of exogenous risk factors. Subsequent studies using expanded population cohorts have now conclusively demonstrated alterations in previously unrecognized genes regulating angiogenesis, vasculogenesis, stem cell differentiation, and cell cycle progression. Although only 4 GWAS to date have analyzed enough participants (>3000 cases and controls) to identify SNPs associated with IAs at genomically significant thresholds (P value ≤1×10-7), future large-scale analyses will be powered to discover rarer risk loci and implicated genes. Furthermore, a more comprehensive understanding of independent and interdependent molecular pathways germane to IA formation and rupture may guide physicians 1 day in developing targeted therapies and optimizing prognostic risk assessment. In this review, the authors present the most up-to-date findings from GWAS of IAs, and discuss the implications of these discoveries for future diagnostic and therapeutic management.

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literature through gene expression and genome-wide linkage analyses are type III collagen (COL3A1), endoglin (ENG), fibrillin (FBN1), α1-antitrypsin (SERPINA1), and polycystin (PKD1, PKD2). Many of the proteins affected are intimately involved in the pathobiology of IAs through regulation of extracellular membrane remodeling in cerebral blood vessels, supporting observations of increased IA formation risk in individuals with connective tissue disorders. Other studies have demonstrated differential expression of genes related to macrophages, lymphocytes, and interleukins, strengthening the argument that immune and inflammatory responses are complimentary pathogenic factors in IA formation.

However, these results are difficult to interpret because of challenges in harvesting healthy tissue for comparison, with many studies relying on control samples from the superficial temporal and middle meningeal arteries. Moreover, it is unclear whether these gene expression alterations are causative in IA formation or rather in response to hemodynamic shear stress trauma and inflammatory cytokine production.

**Methodology of GWAS**

The advent of GWAS was preceded by a number of major collaborative and technological revolutions in the scientific world. The collective efforts of multiple international consortia identified millions of common SNPs and copy number polymorphisms in the DNA of populations from various ancestries and linkage-disequilibrium patterns, establishing a benchmark for future disease-oriented GWAS. In addition, the advancement of high-throughput, multiplex genotyping arrays afforded the opportunity to sequence hundreds of thousands of SNPs using silica bead- and chip-based platforms at dramatically lower costs, although improving coverage and specificity.

Most GWAS of IAs have been conducted in a case–control (binary) setup, often in 2 distinct phases. In the initial discovery phase, cases (those with IAs) and controls are genotyped, and population stratification is prevented by comparing genome-wide allele frequencies with those of corresponding ethnic groups from the HapMap data set (http://hapmap.ncbi.nlm.nih.gov). After adjusting for false-positives and permutation testing, SNPs passing quality control filters that reach a preset significance threshold are genotyped in separate, independent cohorts during the replication phase. Genotyping data can be combined from these independent groups to produce a meta-analysis, and subsequently logistic regression analysis is performed to predict the probability of IA given a specific SNP. Odds ratios (OR) and PPAs ranging from 0.72 to 0.98 (Table I in the online-only Data Supplement).

GWAS of IAs

In 2008, Bilguvar et al22 published their landmark study on the largest GWAS of IA to be published at that time. Their analysis and methods set the stage for future GWAS to build on, and provided additional insight into genomic regions associated with these lesions. The authors used Finnish and Dutch (European) cohorts to comprise the discovery group, which identified candidate SNPs that were subsequently genotyped in 2, pooled Japanese replication cohorts. In total, the study analyzed 2196 cases and 8085 controls. After combining data sets from both groups, SNPs localizing to 3 loci passed the genomic significance threshold. These loci were 2q33.1 (OR, 1.24; \( P=4.4\times10^{-10} \)), 8q11.23 (OR, 1.36; \( P=1.4\times10^{-10} \)), and 9p23.1 (OR, 1.29; \( P=1.4\times10^{-10} \)). These loci are associated with BOLL and PLCLI genes, respectively.

In a follow-up study by the same group, Yasuno et al34 added additional cohorts to increase their study population to a monumental 5891 cases and 14181 controls, the largest GWAS of IAs to date. Their data strengthened the association of IAs with SOX17 (OR, 1.28; \( P=1.3\times10^{-12} \)) and CDKN2A-CDKN2B (OR, 1.32; \( P=1.5\times10^{-12} \)), whereas the BOLL and PLCLI genes on the 2q locus were not validated. In addition, SNPs in genes in the vicinity of 3 new loci were described, including CNNM2 (OR, 1.29; \( P=1.2\times10^{-9} \)), STARD13 (OR, 1.20; \( P=2.5\times10^{-9} \)), and RBEBP8 (OR, 1.22; \( P=1.1\times10^{-12} \)). With the dramatically increased cohort size, this study was powered to detect 89% of variants with a genomic relative risk of 1.25 (compared with 80% in their previous study). Subsequently, Yasuno et al35 published an expanded analysis using discovery data from this study. Their initial work only replicated genomic regions that contained SNPs with a posterior probability of association >0.5, signifying a high likelihood of true risk association with aneurysm development. To identify additional risk loci, their group genotyped 25 SNPs within 14 loci that demonstrated a posterior probability of association of 0.1 to 0.5 in the discovery cohort from their 2010 study in 2 Japanese replication cohorts of 3111 cases and 1666 controls. Significant associations were discovered with 3 additional loci, implicating the EDNRA (OR, 1.22; \( P=2.2\times10^{-8} \)), NDUFA12/NR2C1/FGD6/VEZT (OR, 1.16; \( P=1.1\times10^{-7} \)), and RRBP1 (OR, 1.20; \( P=2.5\times10^{-9} \))35 demonstrating PPAs ranging from 0.72 to 0.98 (Table I in the online-only Data Supplement).

Although these previous reports incorporated genotype data from an admixture of European and Japanese ancestries, a report by Akiyama et al36 focused on analyzing SNPs singularly within the Japanese population. After adjusting for sex effects in a group of 1027 cases and 853 controls, SNPs within 4 loci were found to be associated with IAs. However, none of these variants reached genomically significant thresholds, which may have been attributed to the smaller sample size used for analysis. Recently, however, Low et al37 performed the largest Japanese-only cohort to be examined by GWA methods. They discovered a SNP in EDNRA (OR, 1.25; \( P=9.6\times10^{-8} \)) that was more significantly associated with IA than evidenced by prior studies. They also identified 2 previously unreported genes that were strongly associated, although not significant, with IAs, including BET1L (OR, 1.25; \( P=3.0\times10^{-6} \)) and ALDH2 (OR, 1.24; \( P=2.6\times10^{-6} \)).
Finally, the most recent GWAS of IAs by Foroud et al\textsuperscript{38} genotyped a European-only population consisting of 2 separate groups: the first group composed of only familial cases, and a second group composed of familial and sporadic cases. Although neither discovery group generated genomically significant results, a meta-analysis of the 2 groups consisting of 1483 cases and 1683 controls yielded genome-wide significance for SNPs in \textit{CDKN2BAS} (OR, 1.36; \(P=3.6 \times 10^{-8}\)), further strengthening this locus’ association with IA. A SNP in \textit{SOX17} also demonstrated moderate association (OR, 1.25; \(P=8.7 \times 10^{-5}\)), albeit weaker compared with previously reported findings. The authors also performed a subanalysis uniquely focusing on the risk of smoking in the context of these 2 susceptibility loci. However, their logistic model demonstrated that the risk of IA with smoking in conjunction with variants in \textit{SOX17} and \textit{CDKN2BAS} was multiplicative (as would be expected by combining any 2 risk factors), suggesting that there is no unique susceptibility to IA on the basis of combination of genetic signature and this modifiable risk factor.

In contrast to prior studies that controlled for hypertension in study populations, Gaál et al\textsuperscript{39} recently examined IA risk loci in individuals originally selected for GWAS of hypertension. The authors genotyped a total of 19 loci previously reported to be associated with IA in Finnish cohorts that had documented elevations in systolic, diastolic, and mean arterial pressures. Their analysis demonstrated that the 5q23.2 locus, encompassing the \textit{PRDM6} gene, had the strongest association with IA in the discovery group, and the association was strengthened after replication in a multinational cohort (\(P=6.8 \times 10^{-5}\)). Interestingly, the 5 most significant candidate loci previously described demonstrated weak associations, suggesting that hypertension-induced IAs may be under the control of distinct genetic mechanisms. Although the 5p23.3 locus has been moderately associated, but not genomically significant with IA in prior studies, this consistent finding presents an attractive candidate to further elucidate the relationship between hypertension and the development of IAs.

Genomic Variants and IA Rupture Status

Because the natural course of most IAs does not end in rupture, it is important to delineate the influence of genetic factors that influence this outcome. In each of the large-scale GWAS of IAs, stratification of individuals based on rupture status did not change the OR for the highest risk alleles within each loci, suggesting that each of these susceptibility variants may be limited in predicting those at highest risk. In contrast, other targeted genotyping studies have demonstrated that SNPs within the \textit{CDKN2A-CDKN2B-CDKN2BAS} genes are associated with aneurysmal rupture. Olsson et al\textsuperscript{40} examined a Swedish population cohort of 183 patients presenting with aneurysmal SAH and 366 healthy, aged matched controls. After univariate analysis and controlling for smoking and hypertension, the researchers identified a variant within these gene’s locus that was directly significant for aneurysmal SAH (OR, 1.42; \(P=0.01\)). In another study scrutinizing the same region, individuals possessing SNPs in the 9p21 locus were significantly more likely to harbor posterior circulation IAs as opposed to anterior circulation IAs. In fact, the most significantly associated SNP in this region was associated specifically with IAs of the posterior communicating artery.\textsuperscript{41} The significance of this finding is emphasized by the fact that posterior circulation IAs possess a higher risk of rupture and have poorer surgical outcomes compared with those in the anterior circulation.\textsuperscript{42} Collectively, this data suggest that in addition to being strongly associated with IA formation, SNPs within the \textit{CDKN2A-CDKN2B-CDKN2BAS} genes are independent risk factors for aneurysm rupture, and in the future may be used in conjunction with aneurysm size for assessment of surgical candidates.

Molecular Pathogenesis of IA-Associated Genes

The 9p21.3 loci has been the most consistent and significantly associated loci across all large-scale GWAS of IAs. Sequence variants within this region have also been described in myocardial infarction, abdominal aortic aneurysm, and ischemic stroke.\textsuperscript{43} There are multiple related genes within this genomic region that may play a role in the pathogenesis of IA. \textit{CDKN2A} codes for the p16\textsuperscript{INK4a} tumor suppressor gene and has 3 distinct alternatively spliced variants, 2 of which function as inhibitors of cyclin-dependent kinase 4 (CDK4). The third transcript contains an alternate reading frame that stabilizes p53 by inhibiting p53 degradation via E3 ubiquitin-protein ligase Mdm2.\textsuperscript{44} CDK4 and p53 both play vital roles in cell cycle progression at the G1 stage, thus \textit{CDKN2A} is one the most commonly altered genes in human cancers. The \textit{CDKN2B} protein product, p15\textsuperscript{INK4b}, prevents cellular proliferation through induction by transforming growth factor-\(\beta\). Similarly, nearby \textit{CDKN2BAS} (aka ANRIL) is a noncoding RNA that is also involved in transcriptional repression. Genetically engineered models have further demonstrated the deleterious effects of alterations in this region, such that aortic smooth muscle cells from mice with targeted deletion of the 9p21 locus show uncontrolled proliferation and no signs of senescence compared with controls.\textsuperscript{45} Collectively, these results imply that the 9p21 gene cluster is essential for cellular proliferation via various molecular pathways and regulators, and plays a major pathogenic role in multiple vascular diseases.

\textit{SOX17} on chromosome 8q12.1 expresses a protein of the SOX family of transcription factors and has also been strongly implicated in most GWAS of IAs. Global gene expression studies have demonstrated that \textit{SOX17} activates various genes involved in hematopoiesis and erythrocyte differentiation from endothelial cell-derived embryonic and pluripotent stem cells.\textsuperscript{46} This protein also promotes endothelial sprouting, likely through mechanisms upregulating \textit{VEGFR2} expression.\textsuperscript{47} Consequently, \textit{SOX17} overexpression promotes vascular abnormalities in mammalian models, which is reversible by deletion of \textit{Sox17}, ultimately leading to normalization of vessel anatomy.\textsuperscript{48}

Genes found in association with 4q31.22 to 23 (\textit{EDNRA}), 10q24.32 (\textit{CNNM2}), 13q13.1 (\textit{STARD13}), 18q11.2 (\textit{RBBP9}), and 5q23.2 (\textit{PRDM6}) will need to be replicated in subsequent studies, although they provide additional candidates to more comprehensively understand IA pathobiology. \textit{EDNRA} codes for a G-protein–coupled receptor in vascular smooth muscle...
cells. When bound by endothelial cell-produced endothelin-1, this complex maintains cerebral blood vessel resistance through potent vasoconstriction. Polymorphisms in this gene have been linked to refractory migraine headaches, myocardial infarction, and hypertension. In this respect, EDNRA may play a significant role in SAH-induced vasospasm, which is a major cause of mortality in the aftermath of aneurysmal rupture. CNNM2 encodes a member of the cyclin family of proteins and has been associated with renal absorption of magnesium and familial hypomagnesemia. Interestingly, GWAS of hypertension have also identified genomically significant associations with this gene, suggesting that electrolyte imbalances may be a potential mediator of hypertension-induced IA formation.

The STARD13 (DLC-2) protein product is a lipid transfer protein and is a tumor suppressor gene expressed in several tissues, as well as endothelial cells. Mutations in this gene have been extensively described in hepatocellular carcinoma and glioblastoma, specifically through tumor-driven mechanisms resulting in robust collateral circulation. In this regard, genetically engineered knockout mice display a reduction in endothelial cell attachment and migration, suggesting that this protein is vital for vasculogenesis and angiogenesis regulation. RBBP8 is a ubiquitously expressed nuclear protein that interacts with the retinoblastoma protein and breast cancer type 1 susceptibility protein in ways that modify DNA repair and cell cycle checkpoints. Similarly, PRDM6 is an epigenetic, transcriptional regulator expressed in tissues that governs differentiation and proliferation of vascular smooth muscle cells (Figure).

These molecular findings collectively substantiate various themes of cell cycle dysfunction and aberrations in blood vessel formation and repair in the pathogenesis of IAs. The cerebral vessels are unique from other areas of the vasculature in that they lack an external elastic lamina, making them less flexible and more vulnerable to hemodynamic shear stress. Abnormalities in vascular smooth muscle cell proliferation may contribute to abnormalities in the contractile abilities of these vessels, leading to stiffer arteries and a predisposition to outpouring in high pressure areas, such as branch points at the anterior and posterior communicating arteries. Furthermore, excessive proliferation of smooth muscle and endothelial cells through aberrations in cell cycle checkpoint regulators may alter vascular remodeling in response to inflammatory mediators triggered by trauma to vulnerable areas in cerebral vessels. Although gene expression studies of IAs have demonstrated alterations in collagens, matrix metalloproteinases, and tissue inhibitors of matrix metalloproteinases, future studies may focus on the interactions of these factors in the context of baseline genetic defects in vascular cell proliferation.

**Future Directions**

GWAS present an enormous logistical and technological challenge, but have nonetheless yielded valuable insight into multiple loci and genes associated with IAs. Although building a foundation for future studies, the results generated to date still only explain a small percent of familial IAs, and conflicting results for a number of loci implies that larger studies will be required to determine significantly associated SNPs. The continued collaboration of multiple international consortiums may lead to the generation of the so-called mega-analyses that will be powered to detect loci with minimal allele frequencies plus further substantiating current candidates. These studies will identify variants that may be unique to certain ethnic populations, in addition to understanding the complex interactions of behavioral risk factors, such as alcohol and tobacco with genetic signatures. Although the collective results from GWAS have identified previously unrecognized factors, they only represent associations, and the genes identified have not been substantiated as causative of IA. Yet identification of these genomic regions will usher in a new era of genetically engineered animal models of IA, which may not only validate GWA study findings, but also provide a platform for the development of targeted therapies and preclinical screening of candidate drugs. In addition, we are in the midst of another
technological revolution where next-generation sequencing will allow rapid, clinically affordable whole genome sequencing to develop a comprehensive catalog of the genomic landscape of individuals with IAs. As an adjunct to GWA study data, next-generation sequencing will allow the development of individualized management and treatment strategies, ultimately reducing the deleterious effects of IA-associated SAH. Other genetic approaches are also rapidly advancing from the research arena to clinical application, including whole exome sequencing, which is less expensive than next-generation sequencing while maintaining coverage and sequence depth, and copy number analysis, which detects amplification and deletion variations within the genome. In addition, environment-wide association studies have recently adopted GWAS methods to analyze hundreds of environmental risk factors, such as chemical toxicants, pollutants, allergens, bacterial/viral organisms, and nutrients in conjunction with a phenotype of interest. Combined with GWAS data, these studies may provide an unprecedented, comprehensive understanding of the interaction between environmental and genetic risk factors in aneurysm development, as has recently been demonstrated for type 2 diabetes mellitus. With appropriate surveillance in high-risk individuals harboring high-risk SNPs in known susceptibility loci, physicians and surgeons will be able to make informed decisions about which patients will benefit most from early surgical or endovascular intervention.

Disclosures

None.

References


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SUPPLEMENTAL MATERIAL
Supplementary Table I. Genome-Wide Association Studies of Intracranial Aneurysms
<table>
<thead>
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<th>Study</th>
<th>Year</th>
<th>Discovery Cohort</th>
<th>Replication Cohort</th>
<th>SNP-Associated Loci</th>
<th>Candidate Genes</th>
<th>OR Per Allele (95% CI)*</th>
<th>P-Value*†</th>
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<td>Bigulvar et al.¹</td>
<td>2008</td>
<td>1580 Cases, 6276 Controls (European)</td>
<td>494 Cases, 676 Controls (Japanese)</td>
<td>2q33.1</td>
<td>BOLL, PLCL1</td>
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<td>1.29 (1.19-1.40)</td>
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<td>Yasuno et al.²</td>
<td>2010</td>
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<td>3111 Cases, 1666 Controls (Japanese)</td>
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<td>Akiyama et al.³</td>
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<td>Yasuno et al.⁴</td>
<td>2011</td>
<td>2282 Cases, 905 Controls (Japanese)</td>
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<td>Low et al.⁵</td>
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<td>12q24.12</td>
<td><strong>ALDH2</strong></td>
<td>1.24 (1.15–1.34)</td>
<td>2.6 x 10⁻⁶</td>
<td></td>
</tr>
<tr>
<td>Foroud et al.⁶</td>
<td>2012</td>
<td>1480 Cases, 1683 Controls (European)</td>
<td>NR</td>
<td><strong>CDKN2BAS</strong></td>
<td>1.35 (NR)</td>
<td>3.6 x 10⁻⁸†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8q11.23</td>
<td><strong>SOX17</strong></td>
<td>1.25 (NR)</td>
<td>8.7 x 10⁻⁵</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI: Confidence interval; NR: Not reported; OR: Odds ratio; SNP: Single nucleotide polymorphism

*Most significant SNP per gene reported
†Genomically-significant values. Genomic significance is dependent on the number of SNPs genotyped per study. The generally
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