

## Genetics of Intracranial Aneurysms

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Intracranial aneurysms (IAs) are localized dilations of intracranial arteries that are because of weaknesses of the endothelial layer. These dilations vary in size (small aneurysms, <5 mm; medium-to-large aneurysms, 6–25 mm; and large aneurysms, >25 mm) and are classified according to their shapes: either localized sac-like pouches or long dilations that increase the vessels diameter; these shapes are referred to, respectively, as saccular or berry aneurysms and fusiform aneurysms. Most IAs are saccular and typically occur at the arterial branching sites of the circle of Willis. Common sites of saccular IAs include the anterior communicating artery, the posterior communicating artery, internal carotid artery, the middle cerebral artery, and the basilar artery bifurcation. Although the exact pathogenesis of IA remains to be established, several hypotheses have highlighted the contribution of maladaptive vascular remodeling triggered by hemodynamic stress and inflammatory response<sup>1</sup>—a chain of events that would ultimately damage blood vessel walls and lead to IA.

The worldwide prevalence of IA is estimated to be ≈3.2%.<sup>2</sup> Subarachnoid hemorrhage (SAH) accounts for ≈5% of all strokes, and 85% of SAHs are because of aneurysmal ruptures. SAH has an incidence rate of 9 per 10000 persons per year and a fatality rate ≈50%.<sup>3</sup> The incidence of SAH is markedly higher in the Finnish and Japanese populations, but surprisingly, this is not because of the prevalence of IA in these populations.<sup>2</sup> The most common clinical symptoms of aneurysmal SAH are a sudden onset of severe headache with stiff neck, vomiting, and photophobia. Unruptured IAs are usually asymptomatic and are identified through the screening of high-risk individuals or as incidental findings of magnetic resonance imaging, particularly magnetic resonance angiogram, or computerized tomographic studies. The diagnosis of IA is made by magnetic resonance angiogram, computerized tomographic angiography, or classical angiography. The diagnosis of SAH is primarily made using computerized tomography or a lumbar puncture.

Although ruptured IAs explain 85% of SAH cases, it has been observed that 50% to 80% of all IAs do not rupture during the course of a person's lifetime. The prevalence ratio of unruptured IA is significantly higher in women than in men (prevalence ratio, 1.61) and also significantly higher in individuals >50 years of age (prevalence ratio, 2.2).<sup>2</sup> A recent

estimate suggests that 1.8% of European individuals have saccular IA, and the prevalence seems to vary among different populations.<sup>4</sup>

The risk of IA rupture increases with its size, location (particularly in the posterior circulation), shape, smoking habit, excessive alcohol consumption, female sex (women-to-men ratio of SAH was ≈2:1), blood pressure, and history of aneurysmal SAH. Controversies remain on the impact of the IA size because small ones have low annual risk of rupture, and yet 85% to 90% of ruptured aneurysms are small. A possible explanation is that most aneurysms form over a relatively short period of time, during which the risk of rupture is at its highest. If bleeding does not occur, the likelihood of rupture again decreases because of stabilization and hardening.<sup>5</sup>

The risk of saccular IA is also higher in some connective tissue-related genetic disorders. Autosomal dominant polycystic kidney disease is the most common disease associated with saccular IA, with a relative risk of 6.9 (95% confidence interval, 3.5–14). Overall, 5% to 40% of autosomal dominant polycystic kidney disease cases also have IA, and 10% to 30% of these develop multiple IA.<sup>2</sup> Autosomal dominant polycystic kidney disease risk genes *PKD1* and *PKD2* are associated with defects in vascular endothelium, which could lead to aneurysmal formation. Other associated disorders and genes include neurofibromatosis type I, Ehlers–Danlos syndrome, Loeys–Dietz syndrome, Marfan syndrome, hereditary hemorrhagic telangiectasia, and endocrine neoplasia type I.<sup>6</sup> However, the link between some of these diseases and IA remains controversial, so additional research is needed.

A family history of IA is frequently observed, and this suggests genetics to be a major risk factor. When 1 or 2 family members develop IA, the risk of first-degree relatives >30 years old is estimated to be as high as 9.8%.<sup>7</sup> In regards to SAH, 10% of cases are associated with a family history of SAH.<sup>8</sup> The prevalence ratio is also significantly higher (3.4; 95% confidence interval, 1.9–5.9) in patients with positive family history of saccular IA or SAH.<sup>2</sup> IA cases with a family history also seem more likely to develop multiple IAs or have a greater risk of rupture, the outcome of IA after rupture in familial cases is also worse. Nonetheless, studies of familial IAs generally suggest incomplete genetic penetrance with a late disease onset and also involve multifactorial,

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environmental, and stochastic risk factors.<sup>9</sup> A large population-based heritability study estimated the heritability of SAH to be 41% (95% CI, 23.7%–55.5%), suggesting the environmental factors play a significant role in the susceptibility of SAH and IA.<sup>10</sup> Familial aggregation of IA may also correlate with the familial aggregation of smoking and drinking behavior, as well as other environmental factors; therefore, it is important to address such confounding variables in genetic studies. During the years, genetic studies have identified several IA risk genes and loci, but many more risk factors and pathogenic mechanisms remain to be discovered.

### Linkage and Candidate Gene Studies

Linkage studies are based on microsatellite markers or single-nucleotide polymorphisms (SNPs) distributed across the genome, which were the earliest ones to use genome-wide data. Such studies were made using either multiple IA families or a single large IA family. Altogether, 15 loci were reported using this approach (Table 1); among which 5 were replicated by >1 study (1p34.3–36.13, 4q32, 7q11, 19q13, and Xp22).

Candidate genes involved in vascular wall and endothelial cells functions were also tested in case–control association studies of IA, especially genes that were within the loci identified by linkage studies. Several meta-analyses examining such

potential IA candidate genes have suggested an increased IA risk for various markers, which are listed in Table 2.

### Genome-Wide Association Studies

Genome-wide association studies (GWAS) brought IA research into another phase. This approach uses dense SNP arrays (500 000–1 000 000 SNPs) across the human genome to genotype up to tens of thousands of IA cases and controls, with the identification of >20 new IA loci. It has thus far been the most successful approach for the identification of common risk factors in IA (Table 3). In 2008, a first GWAS of IA was conducted using a discovery cohort of 2100 cases and 8000 control individuals of Finnish and Dutch origin and a replication cohort of Japanese origin<sup>11</sup>; this study revealed significant association signals on 2q (*PLCL1*), 8q (*SOX17*), and 9p (*CDKN2A-CDKN2B*). A follow-up independent GWAS used a larger cohort of European and Japanese origin (5891 cases and 14 181 control individuals) and identified 3 new loci: 18q11.2 (*RBBP8*), 13q13.1 (*STARD13*), and 10q24.32.<sup>12</sup> Two loci from the first GWAS<sup>11</sup> (8q11.23–12.1 containing *SOX17* and 9p21.3 containing *CDKN2A-CDKN2B*) were replicated in the follow-up study, and the genes in those loci are known to be involved in cell-cycle progression. The 2q locus was, however, not replicated; therefore, it may be a false-positive finding. It is also noteworthy that the 9p21.3 (*CDKN2A-CDKN2B*)

**Table 1. Risk Loci Reported in the Linkage Studies for Familial Intracranial Aneurysms**

Linkage Loci	Populations	Study Cohort: Affected/ Family (LOD Score)	References
1p34.3–36.13	North American	10/1 (4.2)	Nahed et al (2005) <sup>43</sup>
	Dutch	7/1 (3.18)	Ruigrok et al (2008) <sup>44</sup>
2p13	Dutch	7/1 (3.55)	Roos et al (2004) <sup>45</sup>
4q32	FIA	482/192 (3.5)	Foroud et al (2008) <sup>46</sup>
		866/333 (2.6)	Foroud et al (2009) <sup>47</sup>
5p15.2–14.3	French-Canadian	12/1 (3.57)	Verlaan et al (2006) <sup>48</sup>
5q22-31	Japanese	104 sib-pairs (2.24)	Onda et al (2001) <sup>49</sup>
7q11	Utah	39/13 (2.34)	Farnham et al (2004) <sup>50</sup>
	Japanese	104 sib-pairs (3.22)	Onda et al (2001) <sup>49</sup>
8p22.2	Korean	13/5 (3.61)	Kim et al (2011) <sup>51</sup>
11q24-25	North American	10/2 (4.3)	Ozturk et al (2006) <sup>52</sup>
12p12.3	FIA	866/333 (3.1)	Foroud et al (2009) <sup>47</sup>
13q14-21	French-Canadian	10/1 (4.56)	Santiago-Sim et al (2009) <sup>53</sup>
14q22	Japanese	104 sib-pairs (2.31)	Onda et al (2001) <sup>49</sup>
14q23-31	North American	10/2 (3.0)	Ozturk et al (2006) <sup>52</sup>
17cen	Japanese	127/29 (3.0)	Yamada et al (2004) <sup>54</sup>
19q13	Finnish	48 sib-pairs (2.6)	Olson et al (2002) <sup>55</sup>
		222 sib-pairs (3.16)	van der Voet et al (2004) <sup>56</sup>
	Japanese	41/9 (4.1)	Mineharu et al (2007) <sup>57</sup>
		127/29 (2.15)	Yamada et al (2004) <sup>54</sup>
Xp22	Dutch	7/1 (4.54)	Ruigrok et al (2008) <sup>44</sup>
	Finnish	48 sib-pairs (2.08)	Olson et al (2002) <sup>55</sup>
	Japanese	127/29 (2.16)	Yamada et al (2004) <sup>54</sup>

FIA indicates Familial Intracranial Aneurysm Study; and LOD, logarithm of the odds.

**Table 2. The Meta-Analyses of Candidate Genes Significantly Associated With Intracranial Aneurysms**

SNP	Gene	P Value	OR (95% CI)	Sample Size (Case/Control)	References
rs4646994	<i>ACE</i>	0.000	1.27 (1.13–1.42)	1074/1500	Cun et al (2017) <sup>58</sup>
rs42524	<i>COL1A2</i>	0.078 ( $P_{het}$ )*	1.74 (1.34–2.26)	1542/1424	Gan et al (2017) <sup>59</sup>
rs2856728	<i>ELN</i>	<0.01	0.66 (0.45–0.95)	920/979	Paterakis et al (2017) <sup>60</sup>
rs2070744	<i>NOS3</i>	0.01	1.22 (1.04–1.44)	1182/1349	Paschoal et al (2016) <sup>61</sup>
rs1800956	<i>ENG</i>	0.011	0.65 (0.45–0.94)	1501/2012	Hu et al (2015) <sup>62</sup>
rs251124	<i>VCAN</i>	0.0002	1.26 (1.11–1.46)	696/763	Sathyan et al (2014) <sup>63</sup>
rs1800796	<i>IL6</i>	<0.001	0.29 (0.20–0.44)	1188/4099	Zheng et al (2013) <sup>64</sup>
rs3767137	<i>HSPG2</i>	0.002	1.22 (1.08–1.39)	632/808	Ruigrok et al (2009) <sup>65</sup>

CI indicates confidence interval; and OR, odds ratio.

\* $P$  value of heterogeneity (0.10 significance cutoff).

gene cluster has been identified as a GWAS hot spot in many other common diseases (eg, coronary diseases, type 2 diabetes mellitus, gliomas, and basal cell carcinomas).<sup>13</sup>

After these 2 major GWAS, several smaller studies that were mainly focused on Japanese cases were conducted. The risks loci of the second GWAS<sup>12</sup> were followed up in 2 independent Japanese IA cohorts, which identified a new locus 4q31.23 (rs6841581) near the *EDNRA*.<sup>14</sup> The associations of *EDNRA* (4q31.22)<sup>14</sup> and *CDKN2A-CDKN2B* (9p21.3)<sup>11</sup> with IA were replicated in another larger Japanese GWAS (top SNPs rs6842241 and rs10757272), and the functional assessment of *EDNRA* SNP rs6841581 showed that it affects the expression of *EDNRA*.<sup>15</sup>

A meta-analysis study that examined all major GWAS concluded that the IA risk loci that appear to be consistent are 8q11 (rs10958409;  $P=1.78\times 10^{-15}$ ), 9p21 (rs10757278;  $P=1.59\times 10^{-13}$ ), 4q31.23 (rs6841581;  $P=1.95\times 10^{-8}$ ), 12q22 (rs6538595;  $P=1.12\times 10^{-7}$ ), 20p12 (rs1132274;  $P=8.29\times 10^{-7}$ ), 2q33 (rs1429412;  $P=1.07\times 10^{-6}$ ), and 7q13 (rs4628172;  $P=4.04\times 10^{-3}$ ).<sup>16</sup> GWAS SNPs rs6841581 (4q31.23), rs10958409 (8q11.23), rs9298506 (8q12.1), rs1333040 (9p21.3), rs12413409 (10q24.32), rs9315204 (13q13.1), and rs11661542 (18q11.2) were also investigated in an independent study of genetic risk scores of the sites of IA, and the genetic risk scores of IA were observed to be higher at the middle cerebral artery site in both the Dutch and Finnish cohorts. However, the genetic risk scores of previous GWAS loci were not found to be associated with familial IA in all cohorts, indicating that risk loci of familial IAs may be different from the results of previous GWAS results.<sup>17</sup>

In support of these genetic risk score findings, a GWAS examining populations of European descendants was conducted using familial and sporadic IA cohorts.<sup>18</sup> The 2 discovery cohorts yielded different risk loci, but a meta-analysis confirmed the previous risk loci in 9p21.3 (rs6475606) and 8q (rs1072737). The suggestive loci obtained from the familial discovery cohort were different from any of the previously reported loci: *PDE1A* (rs1897472) and *BTBD16* (rs911774). These 2 loci were, however, not significant after the inclusion of cases from the sporadic discovery cohort, thus reinforcing the idea that familial IA may have different underlying genetic causes.<sup>18</sup>

Focusing on population-specific and low-frequency variants, an IA GWAS conducted using Finnish familial IA cases identified high IA risk loci with low-frequency (minor allele

frequency<0.05) variants on 2q23.3, 5q31.3, 6q24.2, and 2q33.1, whereas 7p22.1 was associated with the number of IAs.<sup>19</sup> Other GWAS focused on different populations also yielded new risk loci. A recent one focused only on European descendants identified new IA risk loci on 7p21.1 (rs10230207),<sup>20</sup> close to the SNP previously associated with ischemic stroke.<sup>21</sup> However, this region failed to show replication in the Finnish cohort,<sup>19</sup> suggesting the genetic heterogeneity of IA might be linked with population diversity. Subsequently, another multi-staged GWAS examining Portuguese IA cases also suggested new loci in this population: rs4667622 (2q31.1), rs6599001 (3p22.2), rs3932338 (5p14.2), and rs10943471 (6q14).<sup>22</sup> Although this study further lengthened the list of GWAS risk loci, it had limited power because of its sample size.

Contrary to the large number of findings, the accounted heritability in these GWAS risk loci is extremely low. For instance, in the Finnish study, all 5 newly discovered risk loci accounted for only 2.1% of the heritability. Additionally, the 6 SNPs identified in the previous GWAS study explained only 2.5% of the heritability in the Finnish population.<sup>19</sup> Besides the possibility that this was because of the lack of power behind some of those studies, the combination of these results suggests that the genetic pathogenesis of IA may likely be population specific or differ between the familial and sporadic forms.

A meta-analysis was conducted using a cohort that combined multiple forms of aneurysms (IA, abdominal aortic aneurysm, and thoracic aortic aneurysm) to identify shared genetic risk factors between these 3 forms of aneurysms. It turned out that despite the fact that these conditions were commonly observed together, no evidence emerged to support a polygenic overlap between these.<sup>23</sup> Another study also discovered that lipid factors and adiposity were associated with abdominal aortic aneurysm and blood pressure with IA,<sup>24</sup> which may further indicate that IA is genetically distinct to other types of aneurysms but perhaps closer to the other cerebrovascular diseases.

## Expression Studies

The use of microarray-based mRNA expression tools to compare IA and control tissues offers a relatively unbiased approach to identify IA candidate genes and reveal pathways. One of the first IA studies to have used this approach revealed enrichments

**Table 3. Loci Significantly Associated With Intracranial Aneurysms Reported in Previous GWAS**

GWAS-Significant Loci	Genes	Top P Value	Populations	Discovery Cohort Patients:Controls	Reference
9p21.3	<i>CDKN2B-AS1</i>	$1.5 \times 10^{-22}$	Finnish, Dutch, Japanese	2100:8000	Bilguvar et al (2008) <sup>11</sup>
			Japanese	1069:904	Akiyama et al (2010) <sup>86</sup>
			Japanese	1383:5484	Low et al (2012) <sup>15</sup>
			North Americans	1483:1683	Foroud et al (2012) <sup>18</sup>
			Finnish, Dutch, Japanese	5891:14 181	Yasuno et al (2010) <sup>12</sup>
			North Americans	2617:2548	Foroud et al (2014) <sup>20</sup>
			North Americans, New Zealanders, Australians	406:392	Deka et al (2010) <sup>67</sup>
			Portuguese	106:101	Abrantes et al (2015) <sup>22</sup>
			Finnish	974:740	Kurki et al (2014) <sup>19</sup>
8q11.23-12.1	<i>SOX17</i>	$1.3 \times 10^{-12}$	Finnish, Dutch, Japanese	2100:8000	Bilguvar et al (2008) <sup>11</sup>
			Finnish, Japanese, Dutch	5891:14 181	Yasuno et al (2010) <sup>12</sup>
			North Americans	1483:1683	Foroud et al (2012) <sup>18</sup>
			North Americans, New Zealanders, Australians	406:392	Deka et al (2010) <sup>67</sup>
7p21	<i>HDAC9</i>	$4.14 \times 10^{-8}$	North Americans	2617:2548	Foroud et al (2014) <sup>20</sup>
	<i>TMEM195</i>		Japanese	1069:904	Akiyama et al (2010) <sup>86</sup>
4q31.22-31.23	<i>EDNRA</i>	$2.2 \times 10^{-8}$	Finnish, Dutch, Japanese	5891:14 181	Yasuno et al (2011) <sup>14</sup>
				1383:5484	Low et al (2012) <sup>15</sup>
12q22	<i>NDUFA12</i>	$1.1 \times 10^{-7}$	Finnish, Dutch, Japanese	5891:14 181	Yasuno et al (2011) <sup>14</sup>
20p12	<i>RRBP1</i>	$6.9 \times 10^{-7}$	Finnish, Dutch, Japanese	5891:14 181	Yasuno et al (2011) <sup>14</sup>
2q32.1	<i>PLCL1</i>	$5.8 \times 10^{-7}$	Finnish, Dutch, Japanese	2100:8000	Bilguvar et al (2008) <sup>11</sup>
2q33	<i>PDE1A</i>	$6.66 \times 10^{-7}$	North Americans	1483:1683	Foroud et al (2012) <sup>18</sup>
10q26.13	<i>BTBD16</i>	$6.69 \times 10^{-6}$	North Americans	1483:1683	Foroud et al (2012) <sup>18</sup>
18q11.2	<i>RBBP8</i>	$1.1 \times 10^{-12}$	Finnish, Dutch, Japanese	5891:14 181	Yasuno et al (2010) <sup>12</sup>
13q13.1	<i>STARD13</i>	$2.5 \times 10^{-9}$	Finnish, Dutch, Japanese	5891:14 181	Yasuno et al (2010) <sup>12</sup>
10q24.32	<i>CNNM2</i>	$1.2 \times 10^{-9}$	Finnish, Dutch, Japanese	5891:14 181	Yasuno et al (2010) <sup>12</sup>
1q23.1	<i>ARHGEF11</i>	$4.93 \times 10^{-5}$ (FPRP*=0.347)	Japanese	1069:904	Akiyama et al (2010) <sup>86</sup>
3p25.2	<i>IQSEC1</i>	$3.63 \times 10^{-5}$ (FPRP=0.391)	Japanese	1069:904	Akiyama et al (2010) <sup>86</sup>
2q23.3	<i>LYPD6</i>	$1.42 \times 10^{-9}$	Finnish	974:740	Kurki et al (2014) <sup>19</sup>
5q31.3	<i>FSTL4</i>	$3.17 \times 10^{-8}$	Finnish	974:740	Kurki et al (2014) <sup>19</sup>
6q24.2	<i>EPM2A</i>	$1.87 \times 10^{-11}$	Finnish	974:740	Kurki et al (2014) <sup>19</sup>
2q33.1	<i>ANKRD44</i>	$1.87 \times 10^{-12}$	Finnish	974:740	Kurki et al (2014) <sup>19</sup>
2q31.1	<i>MYO3B</i>	$7.13 \times 10^{-5}$ (RAS <sub>diff</sub> =13.7%)	Portuguese	106:101	Abrantes et al (2015) <sup>22</sup>
3p22.2	<i>WDR48</i>	$6.05 \times 10^{-5}$ (RAS <sub>diff</sub> =14.7%)	Portuguese	106:101	Abrantes et al (2015) <sup>22</sup>
5p14.2	<i>PRDM9</i>	$2.02 \times 10^{-4}$ (RAS <sub>diff</sub> =13.0%)	Portuguese	106:101	Abrantes et al (2015) <sup>22</sup>
6q14	<i>HTR1B</i>	$5.50 \times 10^{-4}$ (RAS <sub>diff</sub> =13.0%)	Portuguese	106:101	Abrantes et al (2015) <sup>22</sup>

FPRP indicates false positive report probability; GWAS, genome-wide association studies; and RAS, relative allele score.

\*False-positive report probability under different prior probability (<0.5 are significant).

†Relative allele score difference between cases and controls (>13.0% are significant).

in adherent junction, mitogen-activated protein kinases, and Notch signaling pathways.<sup>25</sup> In another study, histocompatibility class-related genes were reported to also be risk factors for the formation of IA.<sup>26</sup> Overall, IA expression profiling studies have highlighted genes whose products are involved in multiple pathways, affecting for instance, cell proliferation, adhesion and migration, extracellular matrix receptor interaction, and cell communication, as well as atherosclerosis, inflammatory response, and apoptosis in the smooth muscle cells.

Other expression studies have used ruptured and unruptured IA tissues and revealed genes encoding members of the MMP (matrix metalloproteinase) family, as well as genes involved in apoptosis, which associated with the rupture. The matrix metalloproteinases 3 (*TIMP-3*) gene appears to be downregulated in unruptured IA, whereas proapoptotic genes are upregulated and antiapoptotic genes are downregulated in ruptured tissues.<sup>27</sup> Ruptured IAs were also reported to have upregulation of various signaling and regulatory genes (eg, toll-like receptor, nuclear factor- $\kappa$ B, hypoxia-inducible factor-1A, and ETS transcription factor family).<sup>28</sup> These results identified dysregulations associated with the development and outcome of IA; however, it is important to remember that some of these are likely not specific to IA arterial tissue and might also be observed in other forms of aneurysms. For instance, genes coding for adhesion proteins of the extracellular matrix (*ICAM1*) and cytoskeleton (*WIPF1* and *TUBA4A*) were reported to be significantly underexpressed in the blood of patients with ruptured IA<sup>29</sup>; suggesting the mechanism of rupture is not only regulated by degenerative process of the arterial wall.

RNA sequencing (RNA-seq) is an approach that uses massive parallel sequencing technologies for transcriptome profiling; a library of cDNA fragments was converted from RNA and sequenced to produce a genome-scale transcription map showing the transcriptional structure and level of gene expression. A recent RNA-seq study identified 229 differentially expressed genes in IA tissues by comparison with controls (intracranial cortical artery tissues); the same study also found the expression of 1489 genes to be modified in ruptured IA in comparison with unruptured IA.<sup>30</sup> Among the pathways affected by genes differentially expressed in IA are those associated with the deposition of extracellular matrix, transmembrane transporter activity, and blood vessel regulation. Genes with Benjamini Hochberg false discovery rate–adjusted *P* values  $<0.05$  are considered differentially expressed. The overexpression of collagen *COL10A1*, cartilage intermediate layer protein *CILP2*, secreted frizzled-related protein *SFRP2*, RNA-binding family member *MEX3B*, and the reduced expression of *FAM134B*, transporter protein *SLC13A3*, coagulation gene *SERPIND1*, growth regulation gene *GREB1*, and gap junction protein *GJB6* are directly linked to these pathways.

Different meta-analyses of IA expression have flagged genes that have repeated expression changes in IA; *BCL2*, *COL1A2*, *COL3A1*, *COL5A1*, *CXCL12*, *TIMP4*, and *TNC* showed differential expression in  $>3$  separate studies.<sup>31</sup> In another meta-analysis where a weighted gene coexpression network analysis was made, it was suggested that the expression of *FOS*, *CCL2*, *COL4A2*, and *CXCL5*, which is linked

to the immune response and extracellular matrix pathways, might associate with the risk of rupture.<sup>32</sup>

Some studies examined the expression of genes that was found to be associated with IA by GWAS, as well as genes in which candidate copy number variations were seen in IA. A copy number variation is a type of structural variant involving changes in the number of copies in a particular gene or region. Two GWAS-significant genes, *CDKN2A*<sup>33</sup> and *SOX17*,<sup>34</sup> were found to be downregulated in IA tissues. The expression of oxidoreductase *WWOX*—a cancer related gene that is in an IA-associated copy number variation—was found to be reduced in IA tissues of Chinese cases.<sup>35</sup> Additionally, a study examining the DNA methylation of IA tissues reported genes encoding cell adhesion molecules and inflammatory pathways to be differentially methylated and expressed during IA development.<sup>36</sup>

Parallel to mRNA studies, specific miRNAs, such as miRNA-183-5p,<sup>37</sup> were also reported as biomarkers in regard to the formation and rupture of IA. miRNAs are small, non-coding RNAs that play critical roles in post-translational gene expression regulation. The differential expression of miRNA has been linked to pathways like apoptosis, vascular wall activation, phagocyte migration, mononuclear leukocyte proliferation, vascular smooth muscle cell modulation, and protein translation machinery.<sup>37</sup>

There are large overlaps in the genes reported to be differentially expressed in IA, ischemic stroke, and arteriovenous malformation blood samples; many of which are involved in the pathways of immune function and hematopoiesis.<sup>38</sup> Thus, there might be shared genetic factors between IA and other cerebrovascular and metabolic diseases.

## Whole Exome Sequencing

The advent of high-throughput sequencing and whole exome sequencing (WES), which started in 2010, opened a major era of genetic research, and it has led to many successful discoveries, especially in rare Mendelian disorders. As a systematic way of exploring rare coding variations, the success rate of WES depends on how much the disease can be explained by those variants and how much the disease exhibits Mendelian inheritance. Despite its wide application in disease gene discovery, the number of WES studies in IA is surprisingly limited, with only 4 studies thus far reported.

The first WES study of IA was reported in 2015, and it examined Japanese families.<sup>39</sup> Twelve families encompassing a total of 42 cases were included in the discovery cohort, promising variants were further examined in a cohort of additional familial and sporadic IA cases. The study identified 78 risk variants and 10 variants across 9 genes (*GPR63*, *ADAMST15*, *MLL2*, *IL10RA*, *PAFAH2*, *THBD*, *IL11RA*, *FILIP1L*, and *ZNF222*) that were further prioritized based on their functions. These 10 variants were genotyped in a validation cohort, and only the variant in *ADAMTS15* (rs185269810, p.E133Q) showed a significant association with familial IA ( $P=0.001$ ). Functional assessment of this variant also highlighted the role of its product in endothelial migration. A subsequent and independent WES study that focused on 7 IA families of European American descent identified 68 potential

risk variants.<sup>40</sup> Linkage analysis and RNA sequencing were applied as additional steps to further select the variants. Disease segregating variants were found in 8 genes (*KLF11*, *ABCC3*, *TANC2*, *ALMS1*, *ARHGAP17*, *SMEK2*, *HTRA2*, and *NDST1*), and RNA-seq revealed only *TMEM132B* to be differentially expressed. Two recent WES studies used a combined WES and targeted resequencing approach. This approach used WES to identify risk genes in large IA families, tested the presence of deleterious variants in a larger cohort of independent IA cases, and assessed the functional impact of the mutant proteins encoded by genes carrying validated variants. Two new potential IA risk genes *THSD1*<sup>41</sup> and *RNF213*<sup>42</sup> were identified: *THSD1* was identified from 9 related patients and validated in 503 IA cases, whereas *RNF213* was prioritized as a risk gene from 6 families (26 patients) and validated in 223 patients with IA. Functional studies on *THSD1* and *RNF213* seemed to suggest impaired endothelial cell focal adhesion and elevating angiogenic activities, which may lead to increased risk of IA through different means.

### Concluding Remark

It is not surprising that none of the genes from the 4 IA WES studies were replicated across each other, and it is also expected that these genes will be distinct from those identified by GWAS. Genetic heterogeneity, phenocopies, or gene–environment interactions are all factors that introduce complexities for the identification of IA genes. IA is a common condition, but the overall genetic findings that emerged from the use of various approaches and large cohorts of familial and sporadic cases point to multiple underlying factors. These genetic factors can act at different levels from the predispositions to IA and their eventual rupture. The inclusion of large IA cohorts and the use of next-generation sequencing looking at rare and intermediate frequency variants represents the next step in the study of IA. This method should be able to identify functional variants that directly contribute to the IA pathogenesis and can be followed up with functional assays. Gene burden tests (ie, sequence kernel association test and variable thresholds) can also be used to perform gene-based association tests. The benefit of this strategy over single variant association test is that it can utilize rare variants and include them in the association study. It is also possible that with the advancing of sequencing technology, single-cell sequencing may be successfully applied to the genetic study of IA because it may identify somatic driver mutations that directly contribute to the growth and rupture of IA. Future genetic studies of IA might also benefit from applying strategies that would focus on populations that have a high prevalence of IA and familial aggregation and from cross-referencing IA risk factors with those reported to promote or affect the development of other cerebrovascular conditions and the inclusion of environmental factors as covariates.

### Disclosures

None.

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## Genetics of Intracranial Aneurysms Sirui Zhou, Patrick A. Dion and Guy A. Rouleau

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