Genetics of intracranial aneurysms

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Abstract

Rupture of an intracranial aneurysm (IA) leads to aneurysmal subarachnoid hemorrhage (ASAH), a severe type of stroke which is in part driven by genetic variation. In the last 10 years, genetic studies of IA have boosted the number of known genetic risk factors, and improved our understanding of the disease. In this review, we provide an overview of the current status of the field and highlight the latest findings of family-based, sequencing, and genome-wide association studies. We further describe opportunities of genetic analyses for understanding, prevention, and treatment of the disease.

Non-standard abbreviations

ASAH: aneurysmal subarachnoid hemorrhage, BP; blood pressure, GRS: genetic risk score, GWAS: genome-wide association study, IA: intracranial aneurysm, MOPD-II: Majewski Osteodysplastic Primordial Dwarfism Type II, MR: Mendelian randomization, SNP: single nucleotide polymorphism, UIA: unruptured intracranial aneurysm, WES: whole exome sequencing.

Introduction

Aneurysmal subarachnoid hemorrhage (ASAH) is a type of stroke caused by rupture of an intracranial aneurysm (IA). It occurs in relatively young people; the mean age is 50 years.[1] Although ASAH is relatively rare constituting only 5% of all strokes,[1] it has a major impact due to its devastating effects: one third of patients dies and one third remains dependent on help.[2] In contrast to the relatively low ASAH incidence, unruptured IA (UIA) are common with a 3% prevalence in the general population.[3]

These UIA often remain undiagnosed until they rupture. ASAH and UIA is one of the few cardiovascular diseases occurring more often in women than men with two third of patients being women.[4,3]

A twin-based study estimated the heritability of ASAH at ~40%,[5] indicative of an important genetic component in the pathogenesis of UIA and ASAH. The heritability is driven by both rare, penetrant mutations as well as common variants with small effect sizes. All common variants combined can currently explain 21% to 29% of the disease[6], whereas the total contribution of rare variants is unknown. Well-established clinical risk-factors for both UIA and ASAH are hypertension and smoking.[7, 8]

In this review we summarize the latest discoveries in the genetics of UIA and ASAH. We discuss Mendelian monogenic disorders with IA as one of their clinical manifestations and the discovery of common, low-frequency and rare genetic variants associated with IA. We also review efforts to translate the findings of these genetic studies to underlying biological mechanisms and discuss how genetic discoveries could help to improve diagnosis, risk prediction, and treatment of patients at high risk for or diagnosed with IA in the future.

Sporadic versus familial intracranial aneurysms

First-degree relatives of ASAH patients have an increased risk of ASAH compared to the general population, and 10% of ASAH patients have relatives who also had an ASAH.[9] In a population-based study, the odds ratio of ASAH for persons with one affected first-degree relative was 2.15 (95% confidence interval 1.77-2.59) compared to sporadic cases, while for persons with two affected first-degree relatives the odds ratio increased to 51.0 (95% confidence interval 8.56-1117).[10] UIA are also more common in patients with a positive family history.[3] Preventive screening for UIA

using Magnetic Resonance Angiography has proven to be cost effective in first-degree relatives of ASAH patients.[11-13] ASAH can subsequently be prevented by endovascular or surgical treatment of the UIA identified with Magnetic Resonance Angiography. Patients with a positive family history (familial cases) more often have ruptured IA of the middle cerebral artery (while sporadic cases usually have these at the anterior communicating artery), have ASAH at a younger age and are more likely to have multiple IA than patients without such a family history (sporadic cases).[14]

Monogenic disorders associated with intracranial aneurysms

Monogenic disorders are caused by penetrant mutations of a single gene, typically displaying Mendelian inheritance patterns. Several monogenic conditions are associated with IA including autosomal dominant polycystic kidney disease,[15] type IV Ehlers-Danlos syndrome (vascular subtype),[16, 17] Marfan syndrome,[16, 18] Loeys Dietz syndrome,[16, 19] and Majewski Osteodysplastic Primordial Dwarfism, Type II (MOPD-II, Table 1).[20-23] As most of the monogenic conditions predisposing to IA are rare, the case series in which UIA and ASAH in these disorders are described are small. Therefore, precise estimates of the occurrence of UIA and ASAH in these disorders are not possible. It is not known to what extent these specific heritable disorders contribute to the entire population of IA patients but they are thought to account only for a very small proportion. Only for autosomal dominant polycystic kidney disease, the condition associated with IA with the highest prevalence in the general population –i.e. 1/1000 individuals-,[24] such an estimate can be made and this disease only accounts for 1.2% of all IA patients.[25]

Genetic studies of intracranial aneurysms

In this review, we focus on genetic studies including markers across the whole genome and briefly mention candidate gene studies. We distinguish three types: 1. Genome-Wide Association Studies (GWAS), aimed at discovering common variants typically with small effect size; 2. low frequency variant association studies in high-risk populations using a similar case/control design as GWAS; 3. family-based studies for the discovery of rare variants with large effect size. These include linkage analysis to discover segregating regions of DNA, and next-generation sequencing to narrow-down potential causal variants. An overview of all identified genetic loci in these studies is show in Figure 1.

Common genetic variants

Thus far, six large (defined as >2,000 cases) GWAS on IA were published.[6, 26-32] Currently, 19 risk loci were identified in these studies combined: 2q33.1, 4q31.22, 5q31.1, 6q16.1, 7p21.1, 8q11.23, 9p21.3, 10q23.33, 10q24.33, 11p15.5, 12p12.2, 12q21.33, 12q22, 13q13.1, 15q25.1, 16q23.1, 18q11.2, 20p11.23, and 22q12.2 (Figure 1, Table 2). Risk loci 2q33.1, 8q11.23 (consisting of two signals), and 9p21.3 were the first found to be associated with IA in a study of 2,075 cases and 6,952 controls.[26] These have been replicated in subsequent studies,[6, 27-29] although the 2q33.1 locus (genetic region harboring an unknown causal variant) was not found in the largest ones.[6, 27, 30] Three risk loci 10q24.32, 13q13.1, and 18q11.2, were found after supplementing the first study to 5,891 cases and 14,181 controls.[27] Applying a more liberal posterior probability of association on the same dataset revealed another risk locus: 4q31.22.[30] These loci were replicated in later studies.[6, 31] A GWAS initiated by the Familial Intracranial Aneurysm study on 2,617 cases and

2,548 controls discovered an additional risk locus on chromosome 7p21.1,[32] which is not yet replicated in other studies. Recently, a meta-analysis including nearly all samples from previous GWAS of IA, and multiple additional cohorts, totaling 10,754 cases and 306,882 controls was conducted.[6] Here, all but two loci (2q33.1 and 7p21.1) were replicated, and eleven new loci were found: 5q31.1, 6q16.1, 10q23.33, 11p15.5, 12p12.2, 12q21.33, 12q22, 15q25.1, 16q23.1, 20p11.23, and 22q12.2.

Several smaller GWAS (including <2,000 cases) were conducted,[28, 33-38] which resulted in the finding of one associated risk variant on locus 3p14.2,[36] which was not found in other GWAS, and replication of the already known loci 4q31.22 and 9p21.3.[28, 31]

In addition to these genome-wide studies, common variants were studied in several candidate gene studies. In a meta-analysis, six variants showed an association with IA: rs42524 (*COL1A2*), rs1800255 (*COL3A1*), rs251124 and rs173686 (*SERPIN3A*), and rs3767137 (*HSPG2*).[39] None of these variants have been confirmed in GWAS so far.

Low frequency genetic variants

Two studies investigated the association of low-frequency variants (minor allele frequency < 5%) with IA.[29, 40] In a study in a Finnish population isolate of 1,615 cases and 6,563 controls variants associated with IA were found on chromosomes 2q23.3, 5q31.3, and 6q24.2. The latter two loci replicated in 717 Dutch cases and 3,004 controls.[29] Another Dutch study on 995 cases and 2,080 controls focusing on protein-coding variants identified *FBLN2* (3p25.1) using a gene-based approach to increase statistical power.[40] This association was not replicated in a European

ancestry cohort of 425 cases and 311 controls, but the strength of association increased in a combined analysis.[40]

Rare genetic variants

The first efforts to find Mendelian risk genes for IA used linkage analysis, and were reviewed before[41]. The identified loci (logarithm of odds >2) are 1p34.3-36.13, 2p13-15, 4q32.2-3, 5p15.2-14.3, 5q22-31, 7q11, 8p22.2, 11q24-25, 12p12.3, 13q14.12-21.1, 14q22-31, 17cen, 19q13.11-13.3 and Xp22.[41] As Next-Generation Sequencing, particularly Whole Exome Sequencing (WES), became available, it was possible to identify rare (typically minor allele frequency < 1%) variants that segregated within families, rather than large genomic segments from linkage analysis. This provided eight potential Mendelian risk genes: *LOXL2* (chr8), *NFX1* (chr9), *ARHGEF17* (chr11), *ADAMTS15* (chr11), *THSD1* (chr13), *RNF213* (chr17), *ANGPTL6* (chr19), and *PCNT* (chr21) (Table 3). The evidence varies per gene. For *ADAMTS15*,[42] *THSD1,*[47] *ANGPTL6*[49] and *ARHGEF17*,[51] functional experiments support their roles in IA. For *PCNT*[52] it was already known that mutations cause MOPD-II which predisposes to IA (Table 1). Rare coding mutations in *LOXL2*[50] and *NFX1*[53] segregated in families with IA, but more evidence to support the involvement of these genes in IA is needed. The mutational burden in *RNF213*[43] was higher in IA cases, indicating that mutations in this gene are risk factors rather than causal variants. *RNF213* is also implicated in other cerebrovascular diseases, being Moya Moya disease,[45] fibromuscular dysplasia[46] and intracranial artery stenosis.[44] Three other WES studies did not result in the identification of risk genes for IA.[54-56]

None of the variants identified in family studies have been found in other populations. Additional rare, damaging, variants in *ANGPTL6*[57] and low frequency

variants in *PCNT*, *RNF213*, *and THSD1* were identified in other populations,[58] but evidence for causality of these additional variants is limited. Therefore, it is yet unknown if these genes have a wide clinical relevance in UIA and/or ASAH.

Translating GWAS to biological mechanisms

One of the main aims of GWAS is to understand the biological mechanisms underlying development and rupture of IA. Below, we summarize the current understanding of biological mechanisms in IA based on GWAS findings.

Mapping GWAS loci to genes

In recent years, several tools were developed to link loci to genes using expression quantitative trait loci (the effect of genetic variants on gene expression of a particular gene) data. In the latest GWAS, expression quantitative trait locus analysis led to the selection of 11 potential causative genes: *SLC22A5*, *SLC22A4*, *P4HA2*, *SOX17*, *NT5C2*, *MARCKSL1P1*, *FGD6*, *NR2C1*, *PSMA4*, *BCAR1,* and *RP11-252K23.2*.[6] *FGD6* and *SOX17* are involved in vascular endothelial cell signaling,[59, 60] suggesting an important role for this cell type in IA. *BCAR1* is a mechanical stress sensor and may contribute to UIA development or rupture through vascular pressure sensing.[61]

Mapping GWAS loci to biological mechanisms

Gene-mapping methods allow gene-set enrichment analysis, but no gene set with a sufficient number of associated genes has been described for IA. Instead, advances in heritability enrichment analysis allows pathway, gene-set and cell-type enrichment directly on summary statistics, without a candidate gene set. In the most recent GWAS, such analyses showed that genomic regulatory regions were enriched, similar to other polygenic diseases.[6] This is in line with earlier findings that IA-

associated single-nucleotide polymorphisms (SNPs) were enriched in regulatory regions of the arteries in the Circle of Willis.[62] Moreover, regions surrounding genes that are specifically expressed in endothelial and/or mural cells (the layer of smooth muscle cells and pericytes) were enriched, supporting findings from an epigenetic study that regulatory regions near IA-associated SNPs were especially active in endothelial cells.[63]

Genetic overlap with other diseases

Studying similarities in genetic causes (known as genetic overlap) with other diseases can help understand the pathogenesis of a disease. In the largest GWAS of IA to date, genetic correlation (ρg) was observed with ischemic stroke (ρg=19.5% ± 7.9% [SE]), deep intracerebral hemorrhage (ρg=51.6% ± 19.8%) and abdominal aortic aneurysms (ρg=30.2% ± 10.5%).[6] Conditioning IA GWAS results on GWAS for blood pressure (BP) and/or smoking pack years (similar to including BP and/or smoking as a covariate in a GWAS), showed that the correlation between IA and ischemic stroke was driven by BP and smoking, while the correlation between IA and deep intracerebral hemorrhage was driven in part by BP and smoking and probably involves additional shared mechanisms. Finally, the correlation between IA and abdominal aortic aneurysms was explained by smoking, but not by BP.

Potential clinical applications

Several efforts have been made to use genetic knowledge to find biomarkers for risk prediction and candidates for therapy of the disease.

Risk prediction

Genetic risk score (GRS), combining risk-associated common genetic variants, can be used to predict risk of complex diseases.[64] So far, few GRS studies in IA have been performed and these used relatively small sample sizes and ≤10 SNPs to construct the GRS.

In the first GRS study of IA, a GRS using seven risk SNPs was not associated with aneurysm size at the time of rupture in 955 Dutch ASAH cases.[65] Later, this study was supplemented with 718 Finnish IA cases, and it was shown that individuals with a higher GRS were more likely to develop an IA on the middle cerebral artery compared to all other arterial locations (odds ratio, 95% confidence interval = 1.54, 1.20-1.98 for highest versus lowest tertile).[66] In another study, identifying 120 IAs in 4,890 individuals from a population cohort, GRS for IA (using 10 SNPs) was associated with aneurysm volume and diameter.[67]

Recently, the explained heritability of IA increased substantially from 5%[30] to 21.6±2.8% or 29.9±5.4% using linkage equilibrium score regression and linkage disequilibrium adjusted kinship, respectively.[6] This means that the explained heritability is over half of the total heritability (40%),[5] potentially allowing better risk prediction for IA. Future studies will show if GRS indeed have predictive value for IA and if clinical implementation of GRS may be useful.

Discovering causal risk factors using genetic data

Most disease risk factor have a (small) genetic predisposition. Mendelian Randomization (MR) mimics the effect of a randomized trial for an exposure (such as blood pressure) on an outcome trait (such as IA), using randomly allocated genetic predisposition for the exposure. This allows assessment of the causal effect that the

exposure has on the outcome. An early MR study including 717 Dutch cases and 1988 controls, did not find MR effects on IA for type 2 diabetes, body-mass index or waist-to-hip ratio adjusted body-mass index.[68] MR analysis of traits measured in the UK Biobank showed causal effects of BP and smoking on IA risk.[6] It was already known that hypertension and smoking are important clinical risk-factors for IA[7, 8] but this MR analysis further underlines the causal involvement of these risk-factors from a genetic perspective. An MR study of genetically determined protein levels found that Scavenger receptor class A, member 5 (*SCARA5;* a ferritin receptor that mediates non-transferrin-dependent delivery of iron) was protective of ASAH and cardioembolic stroke.[69] No predicted MR effect of *SCARA5* on any other disease was found and *SCARA5* could therefore be a promising biomarker for ASAH.

Therapeutic targets

Data-driven approaches combining GWAS data with drug bioactivity data can identify drug classes that target genes associated with a disease and consequently can aid in finding strategies for drug repurposing. Drug targets with human genetic evidence are more likely to lead to approved drugs.[70] Enrichment of GWAS effects in genes targeted by existing drugs in IA showed that anti-epileptic drugs and sex hormones have pleiotropic effects on IA (area under the receiver operating characteristic curve = 0.675 and 0.652, respectively).[6] A limitation of this approach is that the direction of effect cannot be established. Further genetic and epidemiologic studies on shared risk of IA, epilepsy, and sex hormone levels are required to determine whether anti-epileptic drugs or sex hormone-related drugs have therapeutic value in preventing IA development and rupture.

Conclusions

Genetics of IA is an active field in which many discoveries were made in recent years. Family-based studies expanded the number of genes and mutations proven to cause familial IA, while GWASs, especially those performed in large collaborative efforts, have identified 17 independent and replicated loci across the genome with an effect on IA risk. These genetic studies in IA can help understand the causes and biology of IA and identify targets for therapeutic intervention. Important genetic roles for blood pressure and smoking have been proven and vascular endothelial cells have been suggested as drivers of the disease. It was also shown that genes targeted by anti-epileptic drugs and sex hormones are enriched in the largest GWAS performed to date. Sex hormone drug target enrichment is in line with the high prevalence in women but the role of anti-epileptic drugs in IA prevention needs to be investigated further. These findings could provide therapeutic targets for IA.

Findings of WES and GWAS studies can be used in risk prediction. WES assumes penetrant, Mendelian variants that have a high chance of causing a disease. The IA risk genes discovered in WES studies were identified in varying populations. Whether these genes play a role in other populations and whether routine genetic screening is beneficial in individuals at risk, such as family members of ASAH patients, has to be investigated.

GWAS studies assume small effect sizes in common genetic variants. Recent advances in GWAS showed a substantial explained heritability for IA showing an important role for common genetic variants. This opens the possibility for a GRS to detect patients at high-risk of UIA development who could be followed-up for preventive screening. Prediction by GRS can be improved by combining multiple

GRSs of risk factors into one meta-score (metaGRS), which was shown effective for ischemic stroke prediction[71]. It should be noted that most studies of IA genetics were performed in the white European population, some in persons from Asian ancestry, and none in for example persons from African descent. This could lead to a biased understanding of the disease and even worse to refrainment of treatment options derived from genetic findings in ethnic minorities.

In recent years, discoveries in genetics of IA have accelerated. Still, we are only beginning to understand IA genetics. As study sizes and bioinformatic possibilities increase, detailed phenotypes, such as aneurysm location and shape, and disease progression, can be accurately investigated. These advances, as well as large international collaborations will likely further accelerate genetic discoveries in IA

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Disclosures

None

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Figure legend

Figure 1. Overview of all risk loci for IA. Blue bars depict regions found in linkage studies. Red diamonds are genes found in whole exome sequencing studies or burden analysis (Table 3). Text labels correspond to these gene names. Blue dots are lead single nucleotide polymorphisms or copy number variants identified in genome-wide association studies (Table 2).

Table 1. Monogenic disorders associated with intracranial aneurysms

Disease	Genes implicated	Evidence for IA predisposition
Autosomal dominant polycystic kidney disease	*PKD1, PKD2*	10% of patients have UIA.[15]
Type IV Ehlers-Danlos syndrome (vascular subtype)	*COL3A1*	In 12 of 99 (12%) patients screened UIA were found.[16] Patients (n=9,000 more often admitted because of an IA than controls (n=9,000; 0.4 vs 0.09%; p<0.01).[17]
Marfan Syndrome	*FBN1*	In 8 of 59 (14%) patients screened UIA were found.[16] Patients compared to controls (both groups n=13,883) more likely to have ASAH and hemorrhagic stroke (0.3% versus 0.2%) and UIA (0.2% versus 0.1%).[18]
Loeys Dietz syndrome	*TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2*, *SMAD3*	In 7 of 25 (28%) patients screened UIA were found.[16] Cerebral hemorrhage (ASAH and/or intracerebral hemorrhage) in 2 of 90 (7%) patients.
Microcephalic/Majewski's Osteodysplastic Primordial Dwarfism, Type II	*PCNT*	UIA in up to 50% of patients[20-23]

Table 2. Genome-wide association studies of intracranial aneurysms. All SNPs that passed the genome-wide significance threshold of $P<5\cdot10^{-8}$ are reported. The number of cases and controls reported are the numbers used to the reported association statistics. These typically are a meta-analysis of discovery and replication cohort. Annotated gene column shows gene names reported in the original publications. If not described, we reported the nearest gene. *In the study by Hong et al (2019) many SNPs reached $P<5\cdot10^{-8}$, but all loci consisted of single SNPs and no replication was done. Therefore, no SNPs are shown there. rs10958409 and rs9298506 are not in linkage disequilibrium (LD). rs9298506 and rs62516550 are in moderate LD ($r^2=0.21$ in Europeans), but not with rs10958409. rs113816216 and rs4705938 are not in LD.

Year	Population	Cases	Controls	Lead SNP	Locus	Annotated gene	Risk allele	Odds ratio	95% confidence interval
2008	Dutch, Finnish, Japanese[26]	2075	6952	rs700651	2q33.1	*PLCL1*	G	1.24	1.15-1.34
				rs10958409	8q11.23	*SOX17*	A	1.36	1.24-1.49
				rs9298506	8q11.23	*SOX17*	A	1.35	1.22-1.49
				rs1333040	9p21.3	*CDKN2A-CDKN2B*	T	1.29	1.19-1.40
2010	Finnish, mixed European, Japanese[27]	5891	14181	rs9298506	8q11.23	*SOX17*	A	1.28	1.20-1.38
				rs1333040	9p21.3	*CDKN2A-CDKN2B*	T	1.32	1.25-1.39
				rs12413409	10q24.32	*CNNM2*	G	1.29	1.19-1.40
				rs9315204	13q13.1	*STARD13-KL*	T	1.20	1.13-1.28
				rs11661542	18q11.2	*RBBP8*	C	1.22	1.15-1.28
2010	Japanese[33]	1027	853	No genome-wide significant findings					
2010	Japanese[34]	191	282	No genome-wide significant findings					
2011	Finnish, mixed European, Japanese[30]	5891	14181	rs6841581	4q31.22	*EDNRA*	G	1.22	1.14-1.31
2012	Japanese[31]	2431	12696	rs6842241	4q31.22	*EDNRA*	C	1.25	1.16-1.34
2012	European ancestry[28]	1483	1683	rs6475606	9p21.3	*CDKN2B-AS1*	T	1.35	Not reported
2014	Finnish and Dutch[29]	2335	9565	rs74972714	2q23.3	*LYPD6*	C	1.89	Not reported
				rs12472355	2q33.1	*ANKRD44*	A	1.27	Not reported
				rs113816216	5q31.3	*FSTL4*	G	1.66	Not reported

				rs75018213	6q24.2	*EPM2A*	A	1.87	Not reported
				rs1333042	9p21.3	*CDKN2B-AS1*	A	1.31	Not reported
2014	Mixed European ancestry, Dutch and Finnish[32]	4133	7869	rs10230207	7p21.1	*HDAC9*	T	1.21	1.14-1.28
				rs10733376	9p21.3	*CDKN2B-AS1*	NA	1.34	1.23-1.45
2015	Portuguese[35]	200	499	No genome-wide significant findings					
2018	French-Canadian[36]	257	1992	rs1554600	3p14.2	*FHIT*	C	3.86	2.46-6.07
2018	Japanese[37]	176	5742	No genome-wide significant findings					
2019	Korean[38]	250	294	No genome-wide significant findings*					
2020	Mixed European, Finnish, Dutch, British, Japanese, Chinese, French-Canadian, Polish[6]	10754	306882	rs6841581	4q31.22	*EDNRA*	A	0.80	0.77-0.84
				rs4705938	5q31.1	*SLC22A5/SLC22A4/P4HA2*	T	1.13	1.09-1.17
				rs11153071	6q16.1	*FHL5*	A	1.16	1.11-1.22
				rs62516550	8q11.23	*SOX17*	T	1.17	1.12-1.22
				rs1537373	9p21.3	*CDKN2B-AS1*	T	0.84	0.81-0.86
				rs11187838	10q23.33	*PLCE1*	A	0.92	0.89-0.94
				rs732998	10q24.33	*NT5C2/MARCKSL1P1*	T	1.19	1.14-1.25
				rs2280543	11p15.5	*BET1L*	T	1.27	1.19-1.35
				rs11044991	12p12.2	*RP11-664H17.1*	A	0.88	0.84-0.92
				rs2681492	12q21.33	*ATP2B1*	T	1.12	1.08-1.17
				rs7137731	12q22	*FGD6/NR2C1*	T	0.89	0.86-0.92
				rs3742321	13q13.1	*STARD13*	T	0.87	0.84-0.90
				rs8034191	15q25.1	*PSMA4*	T	0.89	0.85-0.93
				rs7184525	16q23.1	*BCAR1/RP11-252K23.2*	A	1.15	1.11-1.19
				rs11661542	18q11.2	*RBBP8*	A	0.87	0.85-0.90
				rs4814863	20p11.23	*SLC24A3*	A	1.11	1.07-1.15

				rs39713	22q12.2	*MTMR3*	T	1.20	1.12-1.28

Table 3. Genes identified in whole exome sequencing studies of intracranial aneurysms. The mutation column shows the identified gene mutation (amino acid change, nucleotide change and SNP ID if available). If applicable, the mutation column shows the lead gene variant identified in the discovery phase of the reported study. Pedigrees/cases shows the number of pedigrees included in the study, as reported in the publication, and the number of cases among all studied pedigrees. N: number of pedigrees / number of cases. SNP: single-nucleotide polymorphism. SNV: single-nucleotide variant. MAF: minor allele frequency.

Gene	N	Population	Locus	Lead mutation	Evidence	Additional mutations	Gene function
ADAMTS15[42]	12/42	Japanese	11q24.2	p.E133Q, c.397G>C (NM_139055.2), rs185269810	-Segregated in 1 family -found in 3 other families. -Replicated in 24 additional familial cases, not in 426 sporadic cases. -Silencing of *ADAMTS15* increased endothelial cell migration.	Not investigated	A disintegrin and metalloproteinase with thrombospondin motif.
RNF213[43]	6/26	French-Canadian	17q25.3	Multiple	-Enriched burden of protein-altering variants in familial cases. -Found a SNP in this gene in a replication cohort of 257 cases and 1,988 controls (odds ratio=1.45, P-value=$7.8 \cdot 10^{-4}$).	rs6565666	-Suggested in vascular wall construction. -The protein contains an AAA-type ATPase domain with E3 ubiquitin ligase activity. -Associated with other vascular diseases.[44-46]
THSD1[47]	1/9	European ancestry	13q14.3	p.R450X, c.1348C>T (NM_018676.3), NA	-In a linkage locus (13q14.12-21.1)[41]. -Variant fully segregated in 9 cases and 13 controls -Thsd1 loss-of-function caused cerebral hemorrhage in zebrafish and subarachnoid hemorrhage in mice.	-p.L5F -p.R460W -p.E466G -p.G600E -p.P639L -p.T653I -p.S775P	-Expressed in endothelial cells of cerebral arteries. -Plays a role in vascular development in zebrafish and mice.[48]

ANGPTL6[49]	1/4	French	19p13.2	p.K460X, c.1378A>T (NM_031917.2), rs769022609	-Selected from 8 variants that were carried by all affected family members. -A statistically significant burden of rare (MAF<1%), nonsynonymous variants in this gene was found in 95 index cases versus 404 controls (P-value=0.023). -Mutated (p.K460X) ANGPTL6 was nearly undetectable in culture medium of HEK293T cell lines, while being expressed in similar amounts as wild-type ANGPTL6. -Serum levels of ANGPTL6 reduced 50% in p.K460X carriers.	-p.E131V -p.L348F -p.A153VfsX66	-Circulating pro-angiogenic factor. -Stimulates endothelial cell migration and endothelial permeability.
LOXL2[50]	1/4	Chinese	8p21.3	p.H45Y, c.133C>T (NM_002318.3), rs142252012	This variant was selected based on gene functions from 15 novel SNVs and 3 rare (MAF<1%) indels that were shared by all affected family members.	Not investigated	The LOX family is involved in crosslink formation in collagens and in elastin, providing strength and elasticity to vascular walls.
ARHGEF17[51]	9/20	Chinese	11q13.4	p.A1465D, c.4394C>A (NM_014786.4), rs2298808	-6 variants in 6 genes segregated in at least 2 families of the discovery cohort, and also found in at least 1 of 86 replication cases. Only ARHGEF17 showed increased burden of rare damaging variants in all cases combined. -Previous studies highlighted ARHGEF17 as a candidate gene for intracranial aneurysms.	-p.R1723Q -p.C1776Y	Activates Rho GTPases, thereby promoting formation of actin stress fibers that play a role in cell shape, polarity, migration, cell-cell and cell-matrix interactions.
PCNT[52]	3/13	European ancestry	21q22.3	p.R2728C, c.8182C>T (NM_006031.6) , rs762890408	2 genes found with rare (MAF<1%), damaging variants segregating within all cases and controls in two families. PCNT was	None	-Centrosome assembly and microtubule formation throughout the cell cycle.

				p.V2811L, c.8431 G>T (NM_006031.6), rs144757781	selected because of its role in MOPD-II.		-Binds intracranial aneurysm risk gene *PKD2.* Risk gene for MOPD-II.
NFX1[53]	1/7	Chinese	9p13.3	p.L840P, c.2518T>C (NM_002504.6), NA	-The only variant found in 7 affected family members and absent in 7 unaffected. -Found in 1 unaffected family member (29 years old).	Not investigated	-Unknown gene function. -Not implicated in cerebrovascular disease before.


1p36.11-36.13
1p34.3-36.13
rs7550260
chr1
2p13-15
rs74972714
rs4667622
rs12472355
chr2
rs9864101
FBLN2
rs6599001
rs1554600
rs78125721
chr3
4q31.3 (CNV)
4q32.2-32.3
rs6841581
chr4
5p15.2-14.3
rs3932338
rs4705938
rs113816216
5q22-31
chr5
rs39713
chr22
rs10943471
rs11153071
rs75018213
chr6
PCNT
chr21
rs7781293
rs10230207
7q11
chr7
rs1132274
rs4814863
chr20
8p22.2
LOXL2
rs10958409; rs9298506
chr8
19q13.3
ANGPTL6
chr19
rs1333040
NFX1
rs1930095
chr9
rs11661542
chr18
10p15.1 (CNV)
rs11187838
rs12413409
chr10
17cen
RNF213
chr17
rs2280543
ARHGEF17
ADAMTS15
11q24-25
chr11
rs7184525
chr16
12p12.3
rs11044991
rs2681492
rs7137731
chr12
rs8034191
chr15
rs9315204
THSD1
13q14.12-21.1
chr13
14q22
14q23-31
chr14
Xp22.2-22.32
chrX