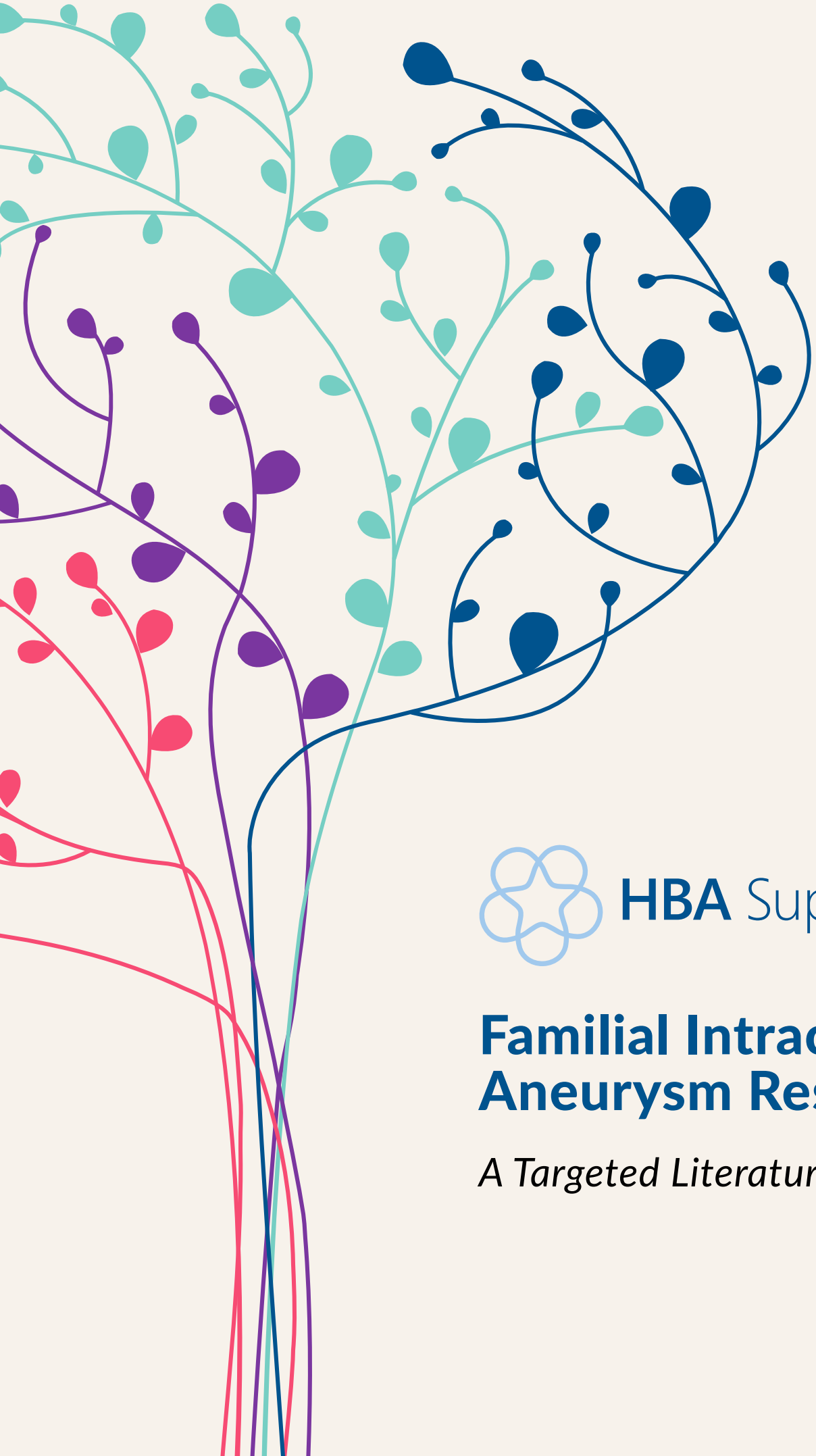


HBA Support

Familial Intracranial Aneurysm Research:

A Targeted Literature Review

JULY 2022

Foreword

Brain, or intracranial, aneurysms are an often symptomless condition which can have a devastating impact on people's lives. Research suggests that a person with a strong family history of intracranial aneurysms (IAs) is up to three times more likely to have the condition than someone in the general population.

Until now, people affected by hereditary brain aneurysms (HBAs), otherwise known as familial intracranial aneurysms (FIAs), have had limited access to resources explaining the condition, its genetic cause and ongoing research. Often they have found themselves trying to piece together information from multiple sources, which can be difficult to navigate and understand. People's experiences of living with familial risk have also played a limited role in research.

This Targeted Literature Review (TLR) provides a robust and accessible source of information for those affected by FIAs, researchers and healthcare service providers. Commissioned by HBA Support and carried out on a pro bono basis by Costello Medical, a healthcare consultancy, this TLR aimed to compile literature on the reported pattern and distribution of FIAs, the genetic causes of FIAs and any current United Kingdom (UK) and global guidelines for their diagnosis, management and treatment. Through conducting the TLR, existing gaps in research and knowledge have been highlighted.

Further research, alongside collaboration between clinicians and those affected by FIAs, will improve the support available to people impacted by the condition. By increasing knowledge and understanding, better genetic testing and targeted screening within high-risk families could be offered, saving lives and minimising the stress and worry which a diagnosis can cause.

HBA Support hopes that this improved accessibility to information and research proves useful for the patient, research and clinical communities. It will provide patients with the ability to make informed choices about their care pathways, including whether or not to request screening, as well as open doors for better dialogue, more research and greater support for the families impacted by this potentially devastating condition. We welcome discussion and look forward to positive conversations through collaboration.

Rebecca Middleton

Founder, HBA Support

HBA Support

HBA Support is a not-for-profit organisation providing information, advice and peer support for people affected by FIAs and their families. We are a patient-focused organisation, providing a platform for people to share their experiences, and working to increase research and understanding of FIAs within the clinical community and wider society.

Contents

Executive Summary

A brain, or intracranial, aneurysm is a bulge in a blood vessel in the brain which has developed due to a weakened blood vessel wall. If an aneurysm ruptures it will typically cause a life-threatening bleed in the brain called a subarachnoid haemorrhage (SAH). There are two types of intracranial aneurysm (IA): Sporadic intracranial aneurysm (SIA) cases occur without any family history of IA, whereas familial intracranial aneurysm (FIA) cases cluster in families.

This Targeted Literature Review (TLR), conducted between November 2021 and January 2022, aimed to provide a clear picture of the current FIA research landscape, as well as available treatment and management guidelines. Multiple online platforms and websites, including electronic databases, were searched for articles addressing three key questions described below.

What is the Pattern and Distribution of IAs?

Globally, the prevalence of unruptured IAs in individuals with a family history of IAs has been recorded as 2.3–29.4%. This was generally higher than the prevalence of unruptured IAs reported in the general population (0.02–8.8%). The annual incidence of unruptured IAs in the general population ranged between 6.1–28.3 people per 100,000.

The annual incidence of ruptured IAs in the general population has been reported as 0.6–25.7 people per 100,000. Within these cases of ruptured IAs, it is not known how many were familial.

Two articles were identified that reported the prevalence and total number of cases of IA in the United Kingdom (UK) specifically, however both were published over 15 years ago. No studies reported the prevalence and incidence of FIAs within the general population, so further research is needed to determine how many people are affected globally.

What Genetic Alterations Cause FIAs?

Variants of more than 30 genes have been suggested to increase susceptibility to FIA development. Six of these genes, all involved in blood vessel wall strength, were implicated in FIAs across two or more studies: *NOTCH3*, *CDKN2BAS*, *SOX17*, *ARHGEF17*, *ANGPTL6* and *LOXL2*.

Despite multiple genetic variants suggested to contribute to FIA susceptibility, there is no 'confirmed' list of genetic candidates that cause FIAs. Further research is needed to consolidate a list of genetic candidates and allow for genetic screening measures to be developed, which could identify high-risk individuals so that preventative treatments could be offered to avoid IA rupture.

What Guidelines are Available for People with FIAs?

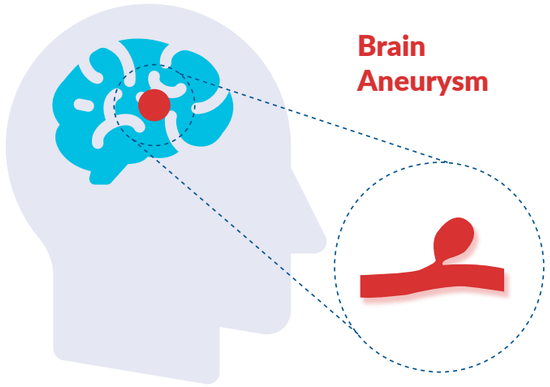
Only one guideline detailed treatment recommendations specific for FIAs, indicating when surgical management should be utilised. As SIA and FIA characteristics vary, the development of more evidence-based, FIA-specific treatment guidelines is needed.

Of the nine identified guidelines making screening recommendations for FIAs, seven indicated that having two IA- or SAH-affected first-degree relatives (a parent, sibling or child) should constitute a 'high-risk individual', whereas two described that one first-degree relative suggests high risk. Alignment on the appropriate approach is therefore needed to ensure those at high risk are detected through screening.

A template guideline developed by the National Institute for Health and Care Excellence (NICE) considered evidence for screening in relatives of adults with SAH. NICE recommended that more evidence is required to support screening and highlighted that explaining the uncertainties surrounding the risks and benefits of screening for IAs to high-risk individuals, is important.

Introduction

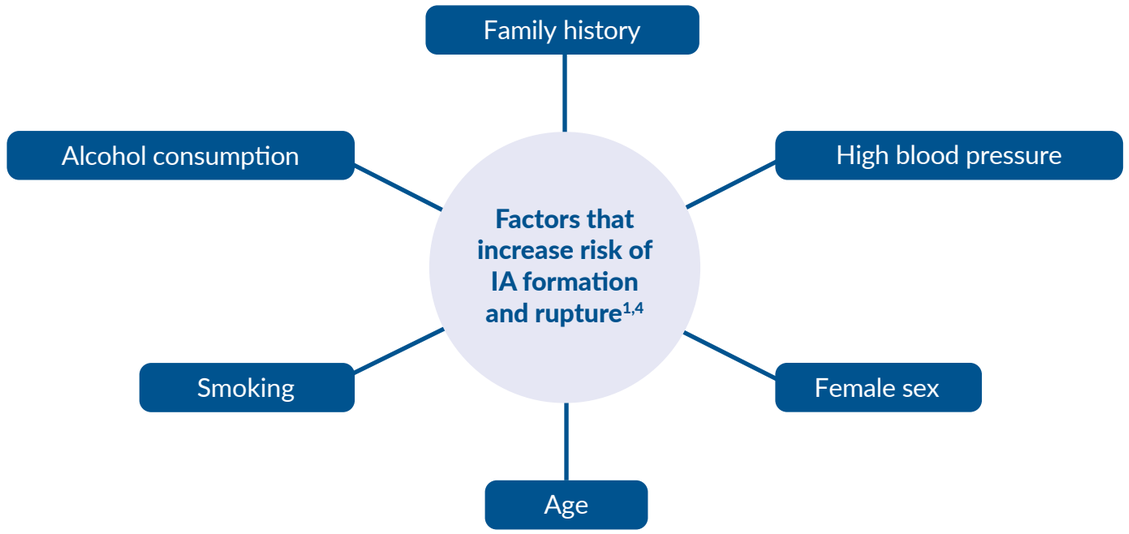
About Intracranial Aneurysms



Brain, or intracranial, aneurysms are a dilation (or a ballooning) in a blood vessel in the brain. The dilation happens because the blood vessel wall is too weak to resist the pressure of blood pushing against it.[1]

Whilst intracranial aneurysms (IAs) often do not cause any symptoms, some individuals can experience headaches and seizures. The rupture of an IA can lead to a potentially life-threatening bleed in the brain, known as a subarachnoid haemorrhage (SAH).[2]

Not all SAH cases are caused by ruptured aneurysms, but most ruptured aneurysms cause SAH.[3] An SAH caused by an aneurysm is known as aneurysmal SAH (aSAH).



Introduction

Some cases of IA occur sporadically, i.e. without a known family history, whereas some cases of IA cluster in families. These cases are known as familial intracranial aneurysm (FIA).[1]

Some genes controlling production of proteins involved in maintaining the health of blood vessel walls, have been associated with IAs.[1,5] Changes in these genes (referred to as 'mutations') result in production of altered proteins, which do not function correctly. This can lead to blood vessel walls being less strong, increasing the chance of IA development. Many members of the same family could develop IAs due to inheriting the same genetic alterations that increase the likelihood of IA formation.[6]

Gene:

A section of deoxyribonucleic acid (DNA) located on a chromosome at a fixed position, that controls the inheritance of particular traits

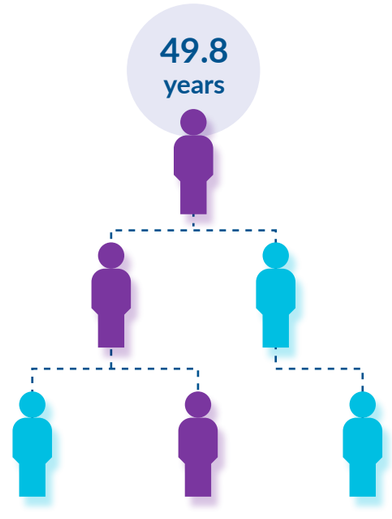
Deoxyribonucleic acid:

A long molecule that carries the instructions for making proteins that the body requires for reproduction, growth, development and general functioning

Average Age at the Time of Aneurysm Rupture[7]

Sporadic Intracranial Aneurysm (SIA) (without strong family history)

Familial Intracranial Aneurysm (FIA) (with strong family history)



Purple signifies an individual with an IA.

Detection

- IAs can be detected through screening before rupture using techniques like Magnetic Resonance Imaging (MRI)[8]
- If the IA is asymptomatic, it can often be detected during screening for other conditions[8]

Treatment

- Doctors may recommend the 'watchful waiting' approach, where the size of the aneurysm is regularly monitored. This is recommended if the aneurysm is small (smaller aneurysms have a lower risk of rupture), or in a specific position[2, 9]
- IA treatment aims to reduce the flow of blood to the aneurysm to reduce the likelihood of rupture. This can be achieved by:[10, 11]
  - » Endovascular coiling
  - » Neurosurgical clipping
  - » Stenting
- When an aneurysm ruptures, a team of specialists must manage any complications[12]
  - » Complications can be severe, for example cerebral ischaemia[13]

Watchful waiting:

The size and shape of the aneurysm is regularly monitored

Endovascular coiling:

Inserting wire into the aneurysm

Neurosurgical clipping:

Placing a small metal clip at the bottom of the aneurysm

Stenting:

Inserting a small mesh tube into the affected blood vessel

Cerebral ischaemia:

A condition which occurs when the brain does not receive enough blood, which can result in brain damage[13]

Objectives and Rationale

This Targeted Literature Review (TLR) aimed to gain a clear picture of the FIA research landscape and guidelines. HBA Support's reach is largely in the United Kingdom (UK) and so guidelines and studies in the UK were of particular interest. The objectives relate to three research streams:

Prevalence and Incidence

IAs are commonly asymptomatic, meaning many remain undiagnosed until rupture, at which point people are at risk of conditions associated with SAH.[10, 13] There is therefore no single estimate of the number of people living with aneurysms globally, and available estimates vary greatly.[14, 15]

This TLR therefore aimed to understand the pattern and distribution (epidemiology) of IAs and FIAs, through investigating the prevalence and incidence as a focus. This would provide a clearer estimate of how many individuals have been impacted by the condition.

Epidemiological studies may also help to determine whether those with a family history of IAs are at a greater risk of developing IAs than those without. This could inform important conversations with families and allow screening to be targeted to those with higher risk.

Genomics

Unlike some diseases caused by an alteration to a single gene, multiple different genetic variants have been associated with FIA development. Though many studies have investigated these genes, there is not a 'confirmed' list of genetic candidates.[1]

This review aimed to summarise genetic candidates implicated in FIA in available genomic studies. Detectable genetic alterations (genomic markers) could help to predict high-risk cases through screening. This would empower individuals with a family history of IAs to access care, which is crucial for those who may have an existing, undetected IA.

National and International Guidelines

National and international guidelines on treating/managing IAs are lacking. Those that are available rarely differentiate recommendations for those with SIAs versus FIAs. There is also lack of clarity around screening for IAs.

This review collated available guidelines, including identifying those specific to the UK, to understand where more FIA-specific recommendations are required.

Summary

What is the pattern and distribution of intracranial aneurysms (IAs)?

Global prevalence of unruptured IAs:

2.3–29.4% in individuals with a family history of IAs

0.02–8.8% in the general population

Global annual incidence of ruptured IAs in the general population:

0.6–25.7 per 100,000 people

What genetic alterations cause familial intracranial aneurysms (FIAs)?

Variants of more than **30 genes** suggested to increase susceptibility to FIAs

more than **20 chromosomal regions** thought to contain variants that increase susceptibility to FIAs

Variants of **6 blood vessel strength genes** implicated in FIAs across 2 or more studies

What guidelines are available for those with familial intracranial aneurysms (FIAs)?

FIA international guidelines:

1 on treatment

9 on screening

Number of first-degree relatives with an IA, aneurysmal subarachnoid haemorrhage (aSAH) or SAH required to recommend screening:

$^{7}/_{9}$ guidelines: 2 or more relatives

$^{2}/_{9}$ guidelines: 1 or more relative

Methods

The TLR was performed using a pre-specified protocol for each stream. Searches were conducted between November 2021 and January 2022.

To identify relevant articles that would answer the key questions of the TLR, multiple online platforms and websites were searched. This included electronic databases, which can be searched for published articles, and the websites of Health Technology Assessment (HTA) bodies. An overview of the study identification process is presented in **Figure 1**.

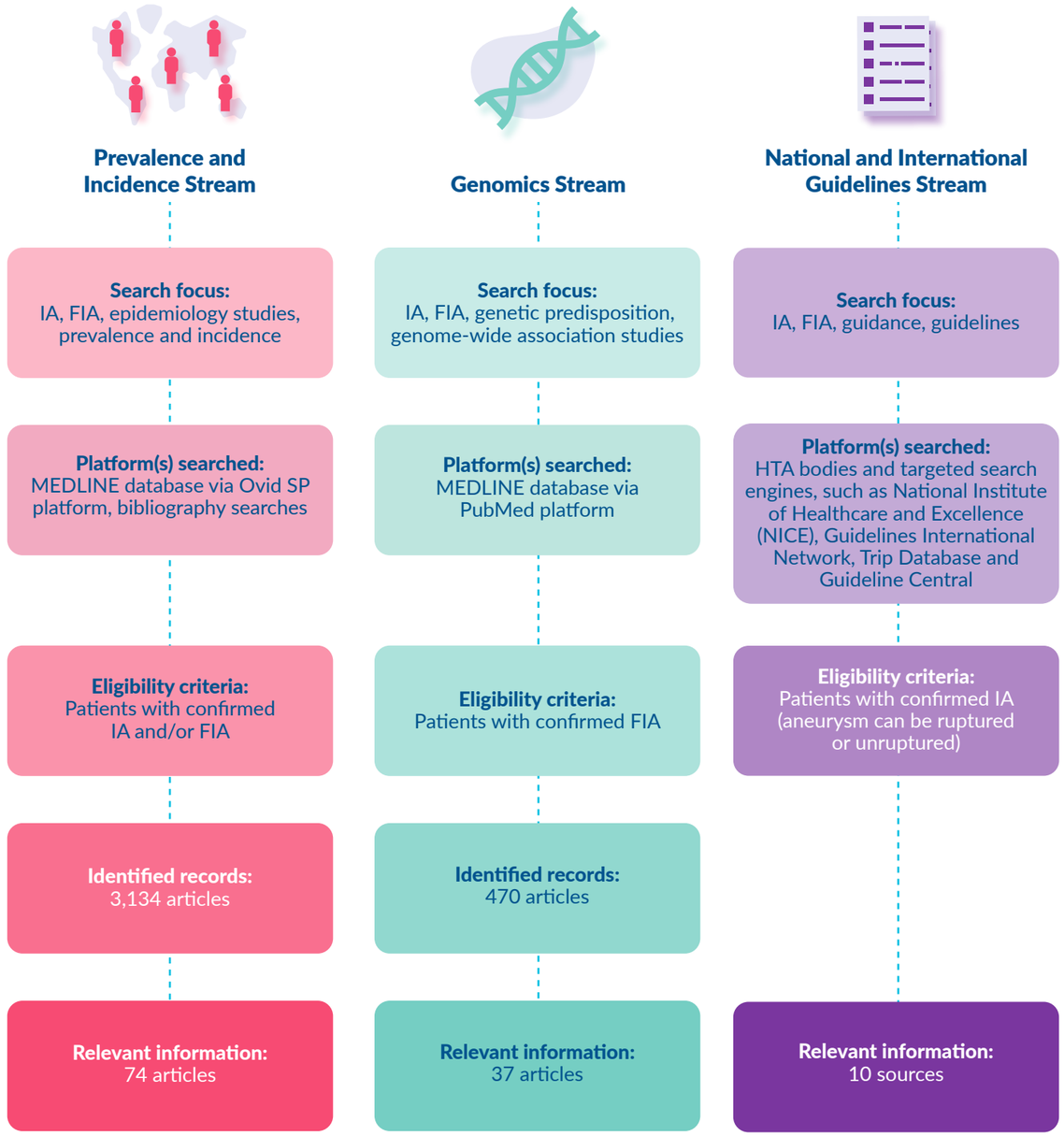
Health Technology Assessment bodies:

Provide recommendations on reimbursement of medicines and other healthcare interventions

For each stream, the relevance of every record identified was checked against pre-specified criteria. Due to a high amount of studies identified, articles were prioritised to ensure only the most relevant information for the TLR was included.

Once the relevant articles had been identified, information that helped to answer the research questions of this TLR was extracted into pre-defined grids for each stream.

Figure 1. Summary of the study identification process across the TLR



A breakdown of the platforms searched to identify relevant articles and sources of information, including detailed search strategies and eligibility criteria, is available from HBA Support in an Appendix, upon request.

01 Prevalence and Incidence

Discussion of Results

Included Studies

74 articles were identified:

- 15 included results on familial cases of IAs ("FIA-specific")
- 61 included results that did not confirm the nature of the IAs ("general")

Included populations varied between studies e.g. a selection of healthy individuals from the general population, or individuals admitted to specialist centres.

In all included studies investigating **IAs**, the prevalence and incidence were calculated **within the general population**.

In contrast, studies of **FIAs** calculated the prevalence **within individuals with a family history** of IAs.

Studies were conducted in **24 countries**, with many based in Japan and Norway due to IAs affecting a high proportion of the population.[16]

Only **two studies** investigated the prevalence and incidence of IAs in the UK.[14, 15]

IA cases were often confirmed through the **collection and review of medical records** and/or **results of diagnostic testing** from patient registries or hospital records. In some studies, autopsies were also conducted.

Included articles reported medical records **from 1951 to 2018.**

Prevalence and Incidence

A summary of the globally reported prevalence and incidence of FIAs and general IAs can be found below (**Figure 2**). Between studies in different countries, there was substantial variation in the reported epidemiology of FIAs and general IAs, as shown in **Figure 3** and **Figure 4**, and **Table 1** and **Table 2**.

No studies were found that reported the epidemiology of ruptured familial cases. Evidence suggests that FIAs have a higher risk of rupture than SIAs.[17] Therefore, the prevalence and incidence of ruptured IAs in individuals with a family history of IAs may be higher than that seen in the general population. A list of studies investigating the risk of rupture can be found in an Appendix upon request.

Epidemiology:

The pattern and distribution of a disease

Incidence:

The probability of a condition occurring in a select population over a given period of time

- **Proportion:** The proportion of an initially disease-free population that develops a condition during a specified period of time. Incidence proportion is calculated as the number of new cases in a given time period divided by the size of the population at the start of the period
- **Rate:** The rate at which cases develop over a specified period of time. Incidence rate is calculated as the number of new cases in a given time period divided by the number of people at risk for the condition

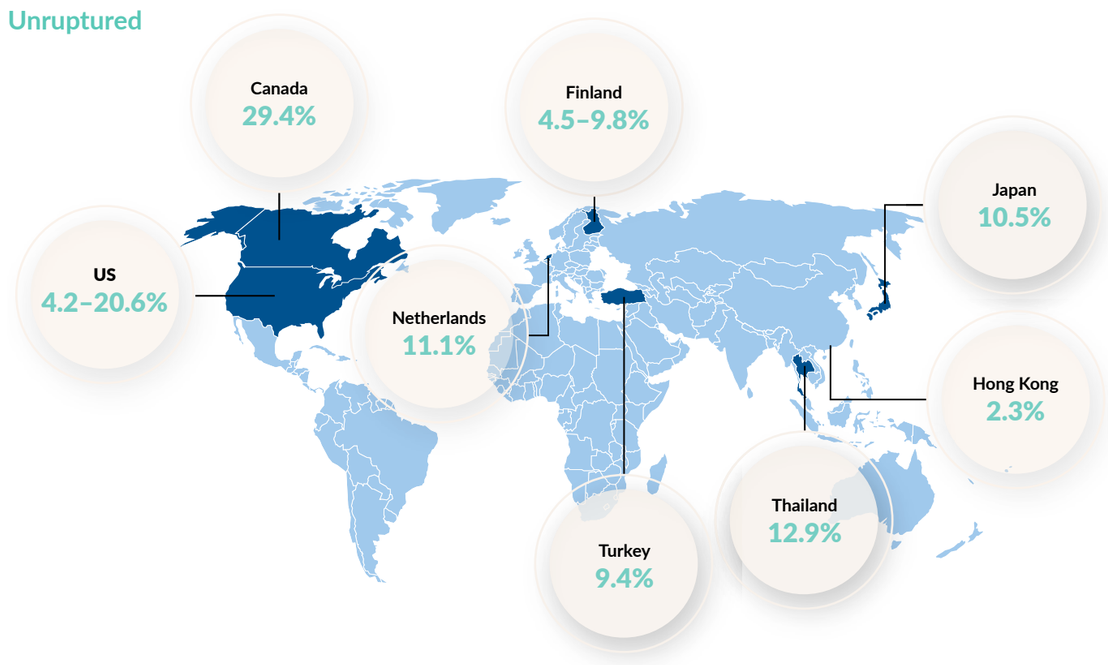
Prevalence:

The proportion of a population with a particular medical condition at a given point in time, normally expressed as a percentage of the population

Figure 2. Reported prevalence and incidence of IAs and FIAs

A beige background signifies the reported epidemiology of FIAs in individuals with a family history of IAs. A blue background signifies the reported epidemiology of IAs in the general population. All incidence proportion values signify the annual number of people with an IA per 100,000 people. All incidence rate values signify the number of expected people with an IA per 100,000 person-years.[14, 16, 18–81]

Figure 3. FIA-specific prevalence in individuals with a family history of IA according to country

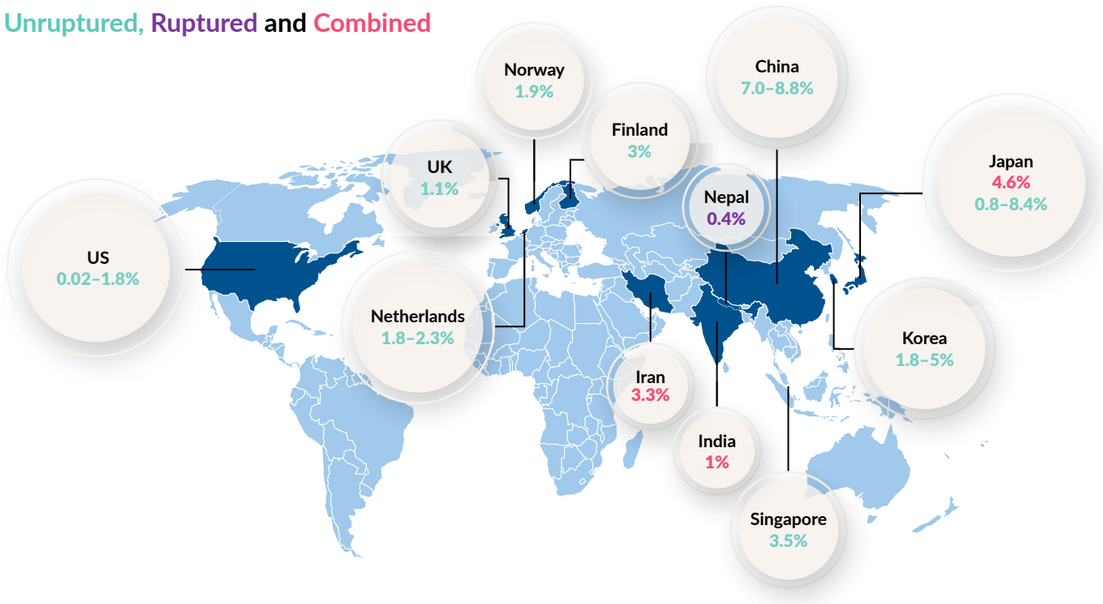


Countries where prevalence has been reported are highlighted in dark blue.[18–28, 47]

Figure 4. General IA prevalence and incidence in the general population according to country

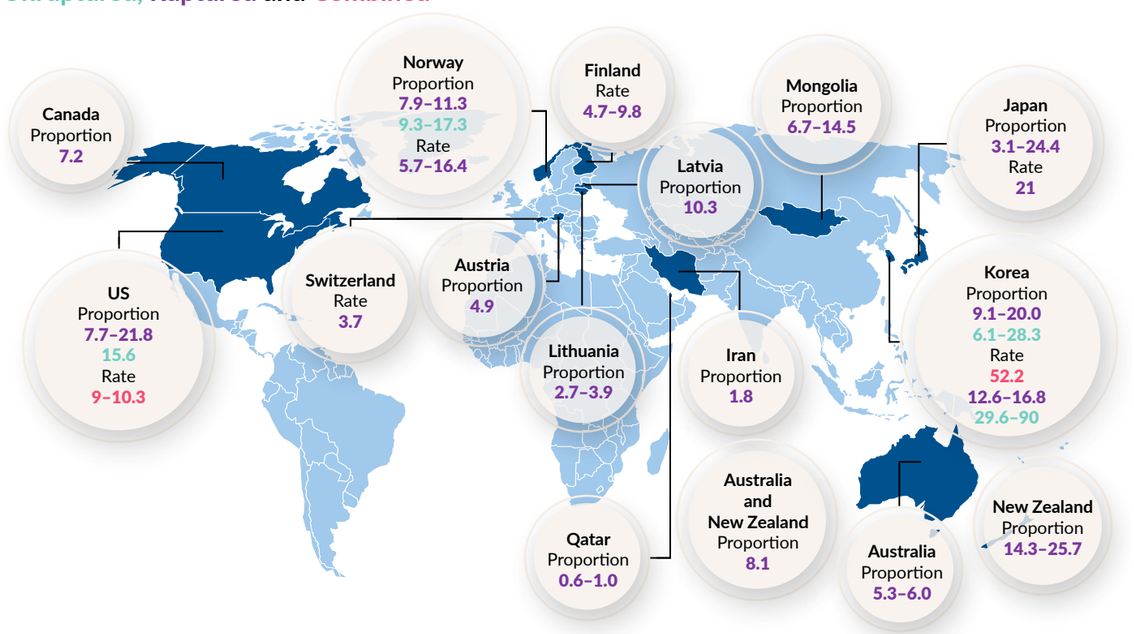
A) Prevalence of general IAs

Unruptured, Ruptured and Combined



B) Incidence of general IAs

Unruptured, Ruptured and Combined



All incidence proportion values signify the annual number of expected people with an IA per 100,000 people. All incidence rate values signify the number of people with an IA per 100,000 person-years.[14, 16, 23, 27, 29–46, 48–81]
Countries where prevalence and/or incidence have been reported are highlighted in dark blue. The size of the circle is not proportionate to the reported prevalence and/or incidence within that country.

Total Number of IA Cases

Most studies recorded the total number of aneurysm cases and used this as the basis for their calculations. However, few studies were able to identify all cases of confirmed aneurysms. Therefore, the total number of people diagnosed with an IA and the number of people living with a known unruptured IA is unknown in many countries.

A UK study reported 7,221 IA ruptures per year based on records from 2005.[15] Given the UK population has grown by ~8 million people since then,[84] this demonstrates the need for updated data regarding the number of IA cases in the UK.

Table 2 presents studies that reported data from several medical centres. These studies were likely to capture more cases than single-centre studies, resulting in a more accurate estimate of the total number of cases per year.[15, 73, 78, 82, 83, 91]

Points that are of relevance to the wider community are highlighted in light pink boxes

Three studies in the United States (US) and Canada investigated the percentage of familial cases in all known IA cases. It was reported that 20% of ruptured and unruptured cases and 20–29% of ruptured cases, were familial.[85, 86, 87]

Subpopulations of Patients with an Aneurysm

A total of 42 studies reported on a subpopulation of patients with an aneurysm (studies are listed in an Appendix, available upon request). These included individuals with:

- Multiple aneurysms
- Different sizes of aneurysm
- Aneurysms in a specific location of the brain

No studies were found that calculated the prevalence and incidence of these specific aneurysm types. Studies instead focused on the proportion of total IA cases that each subpopulation accounted for.

Aneurysm characteristics can impact imaging outcomes and rupture risk, so these factors may be of relevance to assess in future epidemiological studies.[79, 88] For example, evidence suggests there is higher prevalence of multiple IAs and ruptured IAs in the middle cerebral artery in patients with FIAs compared with SIAs.[89]

Table 1. Epidemiology of FIA

IA subcategory	Country	Reported outcomes
Prevalence of IA in individuals with a family history of IA		%
Unruptured	US	4.2–20.6[18–20, 25]
	Canada	29.4[24]
	Netherlands	11.1[a, 26]
	Finland	4.5–9.8[27,47]
	Turkey	9.4[22]
	Japan	10.5[23]
	Thailand	12.9[28]
	Hong Kong	2.3[21]
Percentage of familial cases in total IA cases		%
Combined, ruptured and unruptured	US	20[85]
Ruptured	US	20[85, 86]
	Canada	29[b, 87]

A first-degree relative with an IA was required for an aneurysm to be defined as an FIA in all studies except two. Kojima et al (1998)[23] included individuals with second-degree relatives with an IA, Mathieu et al (1997)[87] included individuals with two or more first- to third-degree relatives. IA: intracranial aneurysm; US: United States.
[a]The value was calculated by dividing the number of individuals with identified IA (51) by the total number of individuals invited to screening (458).
[b]The value was calculated by dividing the number of individuals with FIA (144) by the total number of individuals with IA (502).

First-degree relative:
A person's parent, sibling or child

Table 2. Epidemiology of general IA

IA subcategory	Country	Reported outcomes
Prevalence of IA within the general population		%
Unruptured	UK	1.1[14]
	US	0.02–1.8[29, 30, 45, 46]
	Netherlands	1.8–2.3[31, 44]
	Norway	1.9[41]
	Finland	3[27]
	Japan	0.8–8.4[23, 32–35, 38, 42]
	Korea	1.8–5[36, 37, 79]
	China	7.0–8.8[39, 40]
	Singapore	3.5[43]
Ruptured	Nepal	0.4[51]
Combined, ruptured and unruptured	Japan	4.6[48]
	India	1[49]
	Iran	3.3[50]

IA subcategory	Country	Reported outcomes
Annual incidence proportion of IA within the general population		Per 100,000 people
Ruptured	US	7.7–21.8[30, 72]
	Canada	7.2[61]
	Australia	5.3–6.0[55]
	New Zealand	14.3–25.7[60]
	Australia and New Zealand	8.1[90]
	Norway	7.9–11.3[69, 74, 80]
	Austria	4.9[67]
	Latvia	10.3[57]
	Lithuania	2.7–3.9[71]
	Japan	3.1–24.4[53, 54, 56, 65, 81]
	Mongolia	6.7–14.5[52]
	Korea	9.1–20.0[58, 59]
	Qatar	0.6–1.0[62]
	Iran	1.8[66]
Unruptured	US	15.6[30]
	Norway	9.3–17.3[74]
	Korea	6.1–28.3[59]
Incidence rate of IA within the general population		Per 100,000 person-years
Ruptured	Finland	4.7–9.8[16, 27]
	Switzerland	3.7[70]
	Norway	5.7–16.4[41, 64, 68]
	Japan	21[63]
	Korea	12.6–16.8[73]
Unruptured	Korea	29.6–90[73]
Combined, ruptured and unruptured	US	9–10.3[75, 77]
	Korea	52.2[76]
Total cases of diagnosed IA		Number of cases per year
Ruptured	UK	7,221[15]
	Netherlands	1,248[83]
	Korea	6,389–6,543[73]
	Pakistan	80[a, 78]
	Taiwan	439[82]
Unruptured	Korea	11,256–37,997[73]
Combined, ruptured and unruptured	US	9,000[b, 91]

IA: intracranial aneurysm; UK: United Kingdom; US: United States.
[a]The value was calculated by dividing the total number of recorded IA cases (240) by the number of years that the study spanned (3).
[b]The value was calculated by dividing the total number of recorded IA cases (34,899) by the number of years that the study spanned (20). As the population sample equated to 20% of all US community hospitals, the value was multiplied by 5 to estimate the number of cases across all community hospitals in the US.

02 Genomics

Discussion of Results

Included Studies

In total, 37 studies that investigated the genomics of FIAs were identified. These studies took place across North America, Europe and Asia-Pacific (APAC).

Genomics:

The study of all of a person's genes (the genome)

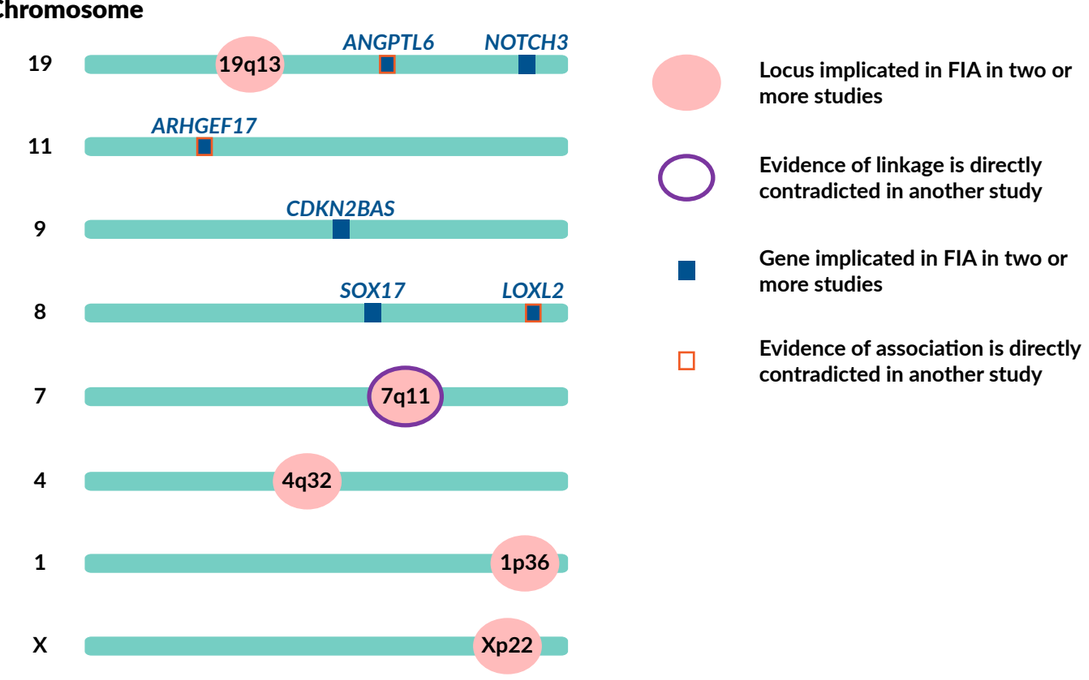
Locus:

In our DNA, genes are located on structures known as chromosomes at a fixed position, known as a genetic locus

Overview of Findings from Genomic Studies

Over 80% of studies provided evidence to implicate several genetic variants or loci in FIA.[4, 5, 92–126] However, there was no standout candidate reported **(Table 3)**. **Figure 5** presents the genetic variants and loci that were implicated in FIA in two or more studies.

Figure 5. Genetic variants and loci implicated in FIA in two or more studies[5, 92, 94–102, 106, 109, 111, 114, 118–122, 124, 127–130]



All genes that were implicated in FIA in two or more studies are involved in blood vessel strength.

Loci may contain genetic variants, which are a permanent change to the DNA sequence that makes up a gene. This change can lead to the production of a protein that does not function correctly resulting in disease. In the case of FIA, the genetic variants may increase an individual's likelihood of experiencing an aneursym.

Genomic studies often consist of association studies or linkage analyses:

Association studies:

Aim to identify genetic variants that increase susceptibility to a particular disease (i.e. a person is more likely to develop the disease because they have these genetic variants)

Linkage analyses:

Aim to find the chromosomal region (the genetic locus) where the genetic variants that increase susceptibility to IAs are located[131]

Under these two categories, four study designs used to find disease susceptibility genes exist:

Genome-wide association studies:

Studies searching across the whole genome for genetic variants that increase susceptibility to FIA

Candidate gene association studies:

Studies searching within a particular gene/set of genes for genetic variants that increase susceptibility to FIA

Genome-wide linkage analyses:

Studies searching the whole genome for the genetic loci of variants that increase susceptibility to FIA

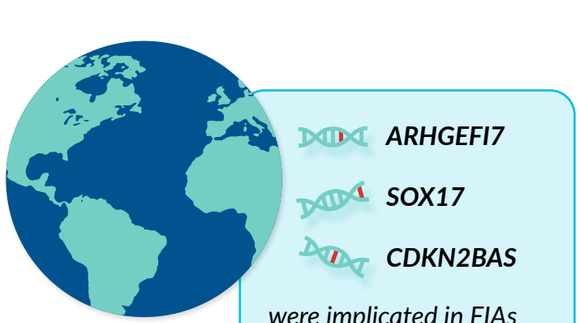
Candidate locus linkage analyses:

Studies searching a particular chromosomal region for the genetic loci of variants that increase susceptibility to FIA

Genetic Variants Implicated in FIA

Across the studies, variants of 38 genes were suggested to contribute to FIA development.[4, 5, 92, 94–97, 99, 102, 103, 106, 109, 110, 117, 118, 120, 123–126]

- There was evidence of an association between FIAs and variants of 14 genes involved in the development, maintenance or integrity of blood vessels in the brain.[92, 94, 95, 97, 98, 102, 106, 109, 116, 117, 123–126]
- Of these genes, six were reported in two or more studies:[92, 94–97, 99, 102, 106, 109, 120, 124]



ARHGEFI7

SOX17

CDKN2BAS

were implicated in FIAs across multiple geographic regions[95, 99, 102]

NOTCH3

LOXL2

were only implicated in FIAs in the APAC region[92, 96, 109, 120]

ANGPTL6

was implicated in FIAs in Europe[94, 106]

Variants of CDKN2BAS, SOX17, NOTCH3, LOXL2, ARHGEF17 and ANGPTL6 were reported in multiple studies. These genes are involved in blood vessel strength, providing a potential link between these genes and FIA development.[92, 94–97, 99, 102, 106, 109, 120, 124]

Loci Implicated in FIA

Across the studies, 21 chromosomal regions were reported to contain genetic variants that could increase susceptibility to FIA.[5, 97, 98, 100, 101, 107, 111, 113–115, 119, 121]

Xp22 **1p36** **7q11** **19q13**

were reported across multiple geographic regions[5, 97, 98, 111, 114, 119, 121]

If loci have been implicated in FIA across different geographical regions, the linkage of FIA to those loci is not specific to one ethnicity.

Some studies reported linkage of FIAs to loci known to contain genetic variants that may be implicated in FIAs. For example, chromosome 8q contains *SOX17*, 7q11 contains *ELN* and 13q14 contains *THSD1*, which are all genes involved in blood vessel strength.[5, 95, 98, 99, 101, 115, 116]

*The existence of blood vessel strength genes **SOX17, ELN, and THSD1** within a chromosomal region implicated in FIA,[5, 95, 98, 99, 101, 115, 116] strengthens the evidence for the association of each of these genes. However, given there may be other genes within these chromosomal regions, these findings alone do not confirm that these genetic variants are associated with FIA.*

There remains no standout disease-causing locus or susceptibility gene in FIA. The genetic variants that cause FIAs differ across geographical regions and between families within the same geographical region. For example, the four genome-wide association studies carried out in North America identified different genetic variants that may increase susceptibility to FIA.[4, 110, 116, 126] In some cases, studies investigating previously-identified IA loci or susceptibility genes could not prove the findings from earlier studies that took place within the same countries.[5, 122]

The findings of genomic studies suggest that multiple different genetic variants may contribute to susceptibility to IAs.[122]

Additional research to consolidate the list of genetic candidates may support genetic screening techniques for families impacted by FIA.

Table 3. Summary of the genetic studies of FIA

Study	Location	Study design				IA population studied	Outcome[a,b]
		Candidate gene association	Candidate locus linkage	Genome-wide association	Genome-wide linkage		
Multiple Regions							
Deka et al (2010)[95]	North America, New Zealand and Australia	✓ 6 genetic variants on 2q33, 8q11 and 9p21	-	-	-	406 unrelated individuals affected by FIA	A variant of ***SOX17*** (on 8q) is associated with FIAs and variants of ***CDKN2BAS*** (on 9p) are potentially associated with IAs
Foroud et al (2008)[101]	North America, New Zealand and Australia	-	-	-	✓	• Study population 1: 412 members of 170 families with FIAs[c] • Study population 2: 482 members of 192 families with FIAs	Chromosomes 4q32, 7q36, 8q12 and 12q21 have evidence of possible linkage with FIAs
Foroud et al (2009)[100]	North America, New Zealand and Australia	-	-	-	✓	1,647 members of 290 families with FIAs	Chromosome 4q32 and 12p12 show possible linkage to FIAs
Foroud et al (2012)[99]	North America, New Zealand and Australia	✓ Variants within 8 loci. Linkage between these loci and FIA has previously been reported (4q31.23, 8q12.1, 9p213, 10q24.32, 12q22, 13q13.1, 18q11.2 and 20p12.1)[95, 102, 132, 133]	-	-	-	• Study population 1: 388 individuals affected by an FIA • Study population 2: 829 and 61 individuals with FIAs and SIAs, respectively	A variant of ***CDKN2BAS*** (on 9p) is associated with FIAs and there is some evidence to suggest a variant of ***SOX17*** (on 8q) is associated with FIAs
Farlow et al (2015)[97]	North America, New Zealand and Australia	-	-	✓	✓	• Genome-wide association: 45 members of 7 families with an FIA • Genome-wide linkage: 2,317 members of 394 families with an FIA	Variants of 15 genes were identified as potentially associated to FIAs including ***ARHGEF17***
Yang et al (2018)[124]	China, Japan and North America	-	-	✓	-	• 20 Chinese individuals with an SIA and an FIA • 86 Japanese, European American and French-Canadian patients with an FIA	Variants of ***ARHGEF17*** increase susceptibility to FIAs
Europe							
Hostettler et al (2021)[106]	UK	✓ *ANGPTL6*	-	-	-	275 individuals affected by an FIA	6 variants of ***ANGPTL6*** are implicated in FIAs
Hofer et al (2003)[104]	Austria and Germany	✓ *ELN*	-	-	-	30 individuals affected by an FIA	No association found between ***ELN*** and FIAs
Hofer et al (2004)[105]	Austria and Germany	✓ *Lysyl Oxisase*	-	-	-	25 individuals affected by an FIA	No association found between ***Lysyl Oxidase*** and FIAs
Sauvigny et al (2020)[118]	Germany	✓ Previously reported unruptured IA and aSAH risk genes (*ADAMTS15*, *ANGPTL6*, *ARHGEF17*, *LOXL2*, *PCNT*, *RNF213*, *THSD1*, *TMEM132B*)[94, 110, 116, 124, 126]	-	✓	- ✓	3 members of a family with a history of an unruptured IA and/or aSAH	No association found between FIAs and previously reported unruptured IA and aSAH risk genes. Variants of ***EDIL3***, *EDNRB*, *DNAH9*, *NEK4 and GGA3* could increase susceptibility to FIAs
Roberts et al (2001)[112]	Ireland	✓ K4 and PN repeats within Apo[a]	-	-		50 members of 3 families with an FIA	No association found between the size of K4 and PN repeats within Apo[a] and FIAs
Bourcier et al (2018)[94]	France	✓ *ANGPTL6*	-	-	-	• Study population 1: 5 members of a family with an FIA • Study population 2: 95 individuals of 6 families with an FIA	One rare coding variant of ***ANGPTL6*** is implicated in FIA susceptibility

Table 3. Summary of the genetic studies of FIA

Study	Location	Study design				IA population studied	Outcome[a,b]
		Candidate gene association	Candidate locus linkage	Genome-wide association	Genome-wide linkage		
Europe							
van der Voet et al (2004)[119]	Finland	-	✓ 19q	-	-	222 affected relative pairs 15 families with FIAs	Chromosome 19q13 is possibly linked to FIAs in the Finnish population
Ruigrok et al (2008)[114]	Netherlands	-	-	-	✓	16 siblings from 1 consanguineous family with an FIA (and their mother), 7 with a confirmed IA	Chromosome Xp22 is linked to FIAs. Chromosome 1p36 has evidence of possible linkage to FIAs[114]
Roos et al (2004)[113]	Netherlands	-	-	-	✓	• Study population 1: 16 members of a consanguineous family with an FIA in 1 generation • Study population 2: 4 non-consanguineous families with FIAs	Chromosome 2p13 is linked to FIAs in the consanguineous family, but not in the other families with FIAs
North America							
Lorenzo-Betancor et al (2018)[110]	US (Florida)	-	-	✓	-	• Study population 1: 13 members of 3 families with an FIA/SAH • Study population 2: 62 individuals with family history of an SAH, 12 with family history of an IA and 26 with family history of both	2 variants of *PCNT* are linked to FIAs
Farnham et al (2004)[98]	US (Utah)	-	✓ 7q11	-	-	39 individuals from 13 extended families with an FIA	Chromosome 7q11 contains susceptibility variants for FIAs
Berthelemy-Okazaki et al (2005)[93]	US (Utah)	✓ *ELN*	-	-	-	16 members of 13 families with an FIA	No association found between ***ELN*** and FIAs
Santiago-Sim et al (2009)[115]	US	-	-	-	✓	32 first-degree relatives of 1 family and 3 unrelated spouses, 10 with an FIA	Chromosome 13q14 is linked with FIAs
Santiago-Sim et al (2009)[117]	US	✓ *TGF-β* and its receptors and coreceptors	-	-	-	44 individuals affected by an FIA	Variants of ***ENG*** and ***TGFβR3*** could increase susceptibility to FIAs
Santiago-Sim et al (2016)[116]	US	-	-	✓	-	36 members of 1 family, 9 with an FIA	Variants of ***THSD1*** could increase susceptibility to FIAs
Powell et al (2019)[4]	Canada	-	-	✓	-	95 members of 6 families with an FIA	2 genetic variants, 1of *C4orf6* and 1 of *SPDYE4*, are associated with FIAs
Zhou et al (2016)[126]	Canada	-	-	✓	-	26 members of 6 families with FC heritage with an FIA	Variants of ***RNF213*** are possibly associated with FIA susceptibility
Asia-Pacific Region							
Ding et al (2020)[96]	China	-	-	✓	-	5 members of 1 family with an FIA, 3 with a confirmed IA	• A variant of *NFX1* is likely to contribute to the development of FIAs • A variant of ***NOTCH3*** is potentially associated with FIAs and should be investigated further
Li et al (2019)[109]	China	-	-	✓	-	20 individuals affected by an IA, 19 with an FIA	3 genetic variants of ***NOTCH3*** are associated with FIAs

Table 3. Summary of the genetic studies of FIA

Study	Location	Study design				IA population studied	Outcome[a,b]
		Candidate gene association	Candidate locus linkage	Genome-wide association	Genome-wide linkage		
Asia-Pacific Region							
Wu et al (2018)[120]	China	-	-	✓	-	• Study population 1: 6 members of 1 family with an FIA, 4 with a confirmed IA • Study population 2: 2 families with an FIA	A variant of ***LOXL2*** may be responsible for a small proportion of FIA cases
Akagawa et al (2007)[92]	Japan	✓ *LOXL1*, *LOXL2*, *LOXL3*, *LOXL4*	-	-	-	185 individuals affected by an FIA	A variant of ***LOXL2*** is associated with FIAs
Hashikata et al (2010)[102]	Japan	✓ Variants within 9p, 2q and 8q	-	-	-	142 members of 31 families with an FIA	A genetic variant of ***CDKN2BAS*** (on 9p) is associated with FIAs
Hirota et al (2016)[103]	Japan	✓ Autosomal dominant polycystic kidney disease genes	-	-	-	150 patients with an FIA	Variants of *PKD1* and *PKD2* could increase susceptibility to FIAs
Krischek et al (2006)[108]	Japan	-	✓ 17cen	-	-	253 members of 106 families with an FIA, including 111 ASPs from 90 pedigrees	No linkage found between 17cen and FIAs
Mineharu et al (2007)[111]	Japan	-	-	-	✓	53 members of 9 families with an FIA, 36 with confirmed IA	Chromosome 19q13 is linked to FIAs
Onda et al (2001)[5]	Japan	✓ *ELN*	-	-	✓	• Linkage analysis: 83 ASPs from 85 families with FIAs • Candidate gene association: 87 and 85 individuals with an FIA and an SIA, respectively	Chromosomal regions 5q22-31, 7q11 and 14q22 have potential linkage to FIAs A polymorphism of ***ELN*** (on 7q11) could indicate risk for IAs in the Japanese population
Yamada et al (2003)[122]	Japan	-	✓ 7q11	-	-	64 members of 14 families with an FIA, 52 with a confirmed IA	No linkage found between 7q11 and FIAs
Yamada et al (2004)[121]	Japan	-	-	-	✓	120 members of 29 families with an FIA, 93 with a confirmed IA	• Chromosomal regions 19q13 and Xp22 are of potential interest • Suggestive linkage exists between chromosome 17cen and FIAs
Yan et al (2015)[123]	Japan	-	-	✓	-	• Study population 1: 42 members of 12 families with an FIA • Study population 2: 24 additional families with an FIA	A variant of ***ADAMTS15*** is associated with FIAs
Yoneyama et al (2003)[125]	Japan	✓ *COL1A2*	-	-	-	115 individuals affected by an FIA	A variant of ***COL1A2*** could increase susceptibility to FIAs
Kim et al (2011)[107]	South Korea	-	-	-	✓	31 members of 5 families with an FIA, 9 with a confirmed IA	Chromosome 8p22 has potential linkage with FIAs

aSAH: aneurysmal subarachnoid haemorrhage; ASP; affected sibling pair; FC: French-Canadian; FIA: familial intracranial aneurysm; IA: intracranial aneurysm; SAH: subarachnoid haemorrhage; SIA: sporadic intracranial aneurysm; UK; United Kingdom; US: United States.
[a]Light purple highlighting of the cells shows when the study found evidence to associate a genetic variant or loci with FIAs. Pink highlighting of the cells shows when the study found no evidence to associate a genetic variant or loci with FIAs.
[b]Genes in bold, italics and red are involved in endothelial cell wall development, maintenance or integrity.
[c]'Families with FIAs' describes families with multiple confirmed or suspected cases of IAs.
[d]*C1orf38, PTAFR, ZNF362, MAP7D1, ROBO3, FOXRED1,TMEM132B, KLF11, ABCC3, TANC2, ALMS1, ARHGEF17, SMEK2, HTRA2, NDST1.*

03 National and International Guidelines

Discussion of Results

Included Guidelines

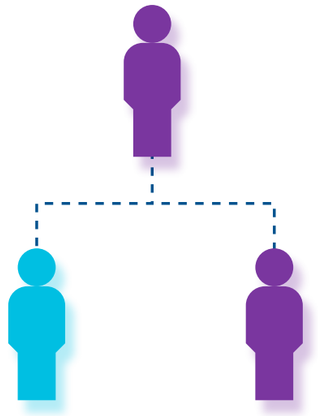
Several guidelines were found that detail appropriate treatment and management for IAs. However, there are few national and international guidelines available that provide specific management and treatment recommendations for FIAs.

The nine FIA-specific guidelines that were identified (see **Table 4**) focused on the screening of individuals in families with multiple IA cases (see FIA-specific Screening Guidelines), with only one guideline commenting on the treatment of FIAs (see FIA-specific Treatment Guidelines).

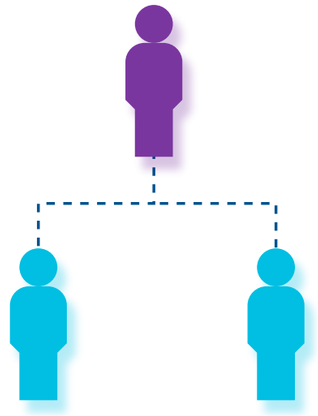
FIA-Specific Screening Guidelines

Nine guidelines made recommendations about when an individual should be offered screening for IAs. These guidelines were based on research demonstrating the increased risk of aneurysm in individuals with family history of IAs. There was some variation between recommendations on how many IA- or SAH-affected first-degree relatives defines a 'high-risk individual', as shown in **Figure 6**. Having a second-degree relative with an IA or SAH is not taken into account when recommending screening.[134–143]

Figure 6. Number of first-degree relatives with IA required to be recommended screening



Seven guidelines suggested a screening test for asymptomatic individuals with **two or more first-degree relatives** with an IA or an SAH[134–141]



Two guidelines suggested a screening test for asymptomatic individuals with **one or more first-degree relatives** with an IA or an SAH[142–143]

Purple signifies an individual with an IA.

In the UK, NICE prepared a guideline for SAH occurring as a result of ruptured aneurysms. This guideline included an evidence review for screening arterial IAs in relatives of adults with an SAH. No relevant clinical studies that compared assessment of first-degree relatives of people with an SAH to no routine assessment were identified in the guideline. However, two health economic evaluations, assessing different screening strategies, were identified and included.

The committee concluded that screening should be made available to people with at least two first-degree relatives who have had an aneurysmal SAH. However, the risks and benefits of screening should be discussed with the individual. In addition, the individual's risk of developing an IA, when taking into account the presence or absence of risk factors, should be considered. Given the lack of evidence to support screening, NICE concluded that further research into this topic is required. In February 2021, the development of the overall guideline document was halted, and so it is still in 'template' format.[134]

Arterial intracranial aneurysm:

An intracranial aneurysm that occurs in the arteries, which are the blood vessels that carry blood from the heart to the rest of the body

National Institute for Health and Care Excellence (NICE):

A body of the Department of Health and Social Care in England that is responsible for providing recommendations on the reimbursement of medicines and other healthcare interventions

FIA-Specific Treatment Guidelines

Only one FIA-specific guideline is available that considers treatment recommendations. The guideline was a clinical decision analysis published in 1992 that only recommends surgical treatment for affected individuals under 70 years old with low or moderate surgical risk.[143]

There is evidence that FIAs have a higher risk of rupture than SIAs and may therefore require a more rigorous treatment regimen to avoid rupture from occurring.[17]

The creation of FIA-specific treatment recommendations would be beneficial to ensure their appropriate management.

Table 4. Summary of guidelines with FIA-specific recommendations

Guideline	Organisations	Geographical breadth	Central topic(s)	FIA-specific recommendations		
FIA-specific screening guidelines for asymptomatic individuals				**Number of first-degree relatives required for individual to be recommended screening**	**Condition the relative must have (IA/ aSAH/SAH)**	**Additional details**
Subarachnoid Haemorrhage due to Ruptured Aneurysms **Evidence Review For Investigating Relatives Of People With Aneurysmal SAH** **(Draft For Consultation) (2021)[134]**	NICE	National (England)	Assessment of the evidence for the clinical and cost-effectiveness of examinations to check for arterial intracranial aneurysms in relatives of adults with an SAH	Two or more	aSAH	• Recommends explaining to patients (and family members) about the uncertainty surrounding the advantages and disadvantages of examining relatives of individuals with an SAH or an IA • The relative's own risk of developing IA should be taken into account (e.g. high blood pressure, whether the individual smokes) • The health economic evidence was not substantial enough to support investigation, and further research into this topic was recommended
Acr Appropriateness Criteria®: Cerebrovascular Diseases-Aneurysm, Vascular Malformation, And Subarachnoid Hemorrhage (2021)[135]	American College of Radiology	National (US)	Guidance on the appropriate imaging of cerebrovascular diseases to detect IAs	Two or more	IA or SAH	NR
Korean Clinical Practice Guidelines For Aneurysmal Subarachnoid Hemorrhage (2018)[136]	Korean Society of Cerebrovascular Surgeons	National (Korea)	Recommendations on the diagnosis and management of an aneurysmal SAH	Two or more	IA or SAH	NR
Clinical Appropriateness Guidelines: Advanced Imaging (2018)[137]	AIM Specialty Health	National (US)	Guidance on head and neck imaging to detect IAs and the requirements pre-imaging	Two or more	IA or SAH	NR
Guidelines For The Management Of Patients With Unruptured Intracranial Aneurysms (2015)[138]	American Heart Association/American Stroke Association	National (US)	Recommendations on the management of patients with unruptured IAs	Two or more	IA or SAH	NR
Clinical Practice Guideline For The Management Of Intracranial Aneurysms (2014)[139]	Korean Society of Interventional Neuroradiology	National (Korea)	Recommendations on the diagnosis and management of IAs	Two or more	IA or SAH	NR

Table 4. Summary of guidelines with FIA-specific recommendations

Guideline	Organisations	Geographical breadth	Central topic(s)	FIA-specific recommendations		
FIA-specific screening guidelines for asymptomatic individuals				**Number of first-degree relatives required for individual to be recommended screening**	**Condition the relative must have (IA/ aSAH/SAH)**	**Additional details**
European Stroke Organization Guidelines For The Management Of Intracranial Aneurysms And Subarachnoid Haemorrhage (2013)[140]	European Stroke Organization	International (Europe)	Recommendations on the diagnosis and management of IAs	Two or more	IA or SAH	• Generally, screening should not be advised in the case of only one affected first-degree relative
Guidelines For The Management Of Aneurysmal Subarachnoid Hemorrhage (2012)[141]	American Heart Association/American Stroke Association	National (US)	Recommendations on the diagnosis and treatment of an aneurysmal SAH	One or more	SAH	NR
FIA-specific screening guidelines for symptomatic individuals				**Guidance**		
American College Of Radiology Acr Appropriateness Criteria® Headache–Child (2017)[142]	American College of Radiology	National (US)	Guidance on the brain imaging of children with headache to detect ruptured IAs	• Brain imaging should be offered to children with severe or unusual head pain with a first-degree relative with IA or another vascular abnormality		
FIA-specific treatment guidelines				**Guidance**		
Familial Intercranial Aneurysms. A Review (ter Berg at al, 1992)[143]	Neurology Department at Twenteborg Hospital Almelo, The Netherlands	Unspecified	Guidance on the management of patients with FIAs	• Surgical treatment is recommended to those under 70 years old with low or moderate surgical risk • Only relatives aged 35–65 years old should be screened, ideally through intra-arterial digital subtraction angiography (a technique used to clearly visualise blood vessels)		

aSAH: aneurysmal subarachnoid haemorrhage; FIA: familial intracranial aneurysm; IA: intracranial aneurysm; NICE: National Institute for Health and Care Excellence; NR: Not reported; SAH: subarachnoid haemorrhage; UK: United Kingdom; US: United States.
Pink shading indicates a screening recommendation; purple shading indicates a management/treatment recommendation.

Outstanding FIA Research Questions

This TLR has addressed key questions relating to the FIA research landscape and guidelines. In doing so, it has highlighted areas where further research is needed, described below. Increased understanding of these areas would inform management and treatment approaches, and help deliver better care to people who need it most:

Prevalence and Incidence

Studies have shown that individuals with a family history of IAs are more likely to have an aneurysm. However, no studies have reported the prevalence and incidence of FIAs within the general population. This would give a valuable insight into the predicted number of total individuals affected by FIAs.

In the UK, only two studies have been conducted which investigate the epidemiology of general IAs. No studies have evaluated the epidemiology of FIAs.

Further research on the prevalence and incidence of FIAs could support the finalisation and update of guidelines for IA screening.

Genomics

Multiple genetic candidates have been associated with FIAs. However, the discrepancies between some studies and the limited understanding of how genetic variants lead to IA development means there is not a confirmed list of genetic candidates that cause FIAs.

Further research into this area may help consolidate the list of genetic candidates and allow for genetic screening techniques to be put into place for FIAs. By identifying aneurysms at risk of rupture, preventative measures can be implemented that could avoid deaths and associated psychological harm.

National and International Guidelines

There are few national and international guidelines available covering the management and treatment of FIAs, meaning that the current clinical approach may be variable. Where guidance is specific to FIAs, it is mostly focused on the screening of high-risk individuals.

Evidence suggests that the characteristics of FIAs differ from SIAs, particularly with a higher risk of rupture of FIAs.[17] Tailored treatment guidelines would therefore be valuable in the UK and globally.

Abbreviations

Abbreviation	Definition
ABCC3	ATP-binding cassette, subfamily C [CFTR/ MRP], member 3
ADAMTS15	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 15
ALMS1	Alstrom syndrome 1
ANGPTL6	Angiopoietin like 6
APAC	Asia-Pacific
APO(A)	Apolipoprotein(a) gene
ARHGEF17	Rho guanine nucleotide exchange factor [GEF] 17
aSAH	Aneurysmal subarachnoid haemorrhage
ASP	Affected sibling-pair
C1orf38	Chromosome 1 open reading frame 38
C4ORF6	Chromosome 4 open reading frame 6
CDKN2BAS	Cyclin-dependent kinase inhibitor 2B antisense RNA
COL1A2	Collagen type 1 a2
DNAH9	Dynein Axonemal Heavy Chain 9
EDIL3	EGF Like Repeats And Discoidin Domains 3
EDNRB	Endothelin Receptor Type B
ELN	Elastin
FC	French-Canadian
FIA	Familial intracranial aneurysm
FOXRED1	FAD-dependent oxidoreductase domain containing 1
GGA3	Golgi Associated, Gamma Adaptin Ear Containing, ARF Binding Protein 3
HTA	Health technology assessment
HTRA2	HtrA serine peptidase 2
IA	Intracranial aneurysm
K4	Kringle 4
KLF11	Kruppel-like factor 11
LOXL1-4	Lysyl Oxidase Like 1-4
MAP7D1	MAP7 domain containing 1
MRI	Magnetic resonance imaging
NDST1	N-deacetylase/Nsulfotransferase [heparan glucosaminyl] 1
NFX1	Nuclear transcription factor
NEK4	NIMA Related Kinase 4
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOTCH3	Neurogenic locus notch homolog protein 3
NR	Not reported
PCNT	Pericentrin
PKD1	Polycystin 1
PKD2	Polycystin 2
PN	Pentanucleotide
PR	Public relations
PTAFR	Platelet-activating factor receptor
RNF213	Ring finger protein 213
ROBO3	Roundabout, axon guidance receptor, homolog 3 [Drosophila]
SAH	Subarachnoid haemorrhage
SIA	Spontaneous intracranial aneurysm
SMEK2	SMEK homolog 2, suppressor of mek1 [Dictyostelium]
SOX17	SRY-box transcription factor 17
SPDYE4	Speedy protein ED
TANC2	Tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 2
TGF-B	Transforming growth factor beta
TGFBR3	Transforming growth factor beta receptor 3
THSD1	Thrombospondin type 1 domain containing protein 1
TLR	Targeted Literature Review
TMEM132B	Transmembrane protein 132B
UK	United Kingdom
US	United States
ZNF362	Zinc finger protein 362

References

1. Bourcier R, Le Scouarnec S, Bonnaud S, et al. Rare Coding Variants in ANGPTL6 Are Associated with Familial Forms of Intracranial Aneurysm. Am J Hum Genet 2018;102:133-141.
2. Williams LN, Brown RD. Management of unruptured intracranial aneurysms. Neurology: Clinical Practice 2013;3:99-108.
3. Sweeney K, Silver N, Javadpour M. Subarachnoid haemorrhage (spontaneous aneurysmal). BMJ Clinical Evidence 2016;2016.
4. Powell AE, Fernandez BA, Maroun F, et al. Familial Intracranial Aneurysm in Newfoundland: Clinical and Genetic Analysis. Can J Neurol Sci 2019;46:518-526.
5. Onda H, Kasuya H, Yoneyama T, et al. Genomewide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. Am J Hum Genet 2001;69:804-819.
6. Wills S, Ronkainen A, van der Voet M, et al. Familial intracranial aneurysms: an analysis of 346 multiplex Finnish families. Stroke 2003;34:1370-1374.
7. Lee JS, Park IS, Park KB, et al. Familial intracranial aneurysms. Journal of Korean Neurosurgical Society 2008;44:136.
8. Novitzke J. The basics of brain aneurysms: A guide for patients. Journal of Vascular and Interventional Neurology 2008;1:89.
9. Wagner M, Stenger K. Unruptured intracranial aneurysms: using evidence and outcomes to guide patient teaching. Critical Care Nursing Quarterly 2005;28:341-354.
10. National Health Service. Brain aneurysm. 2018. https://www.nhs.uk/conditions/brain-aneurysm/. Accessed 23/03/2022.
11. Alkhalili K, Hannallah J, Cobb M, et al. The effect of stents in cerebral aneurysms: A review. Asian journal of neurosurgery 2018;13:201.
12. Diringer MN, Bleck TP, Claude Hemphill J, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocritical care 2011;15:211-240.
13. National Health Service. Subarachnoid haemorrhage. 2021. https://www.nhs.uk/conditions/subarachnoid-haemorrhage/. Accessed 23/03/2022.
14. Keuss SE, Parker TD, Lane CA, et al. Incidental findings on brain imaging and blood tests: results from the first phase of Insight 46, a prospective observational substudy of the 1946 British birth cohort. BMJ Open 2019;9:e029502.
15. Rivero-Arias O, Gray A, Wolstenholme J. Burden of disease and costs of aneurysmal subarachnoid haemorrhage (aSAH) in the United Kingdom. Cost Eff Resour Alloc 2010;8:6.
16. Jalava I, Pyysalo L, Alanen M, et al. Regional differences in the incidence of aneurysmal subarachnoid haemorrhage in Finland. Acta Neurochir (Wien) 2017;159:1657-1662.
17. Mensing LA, Greving JP, Verhoeff TA, et al. Comparison of Rupture Risk of Intracranial Aneurysms Between Familial and Sporadic Patients. Stroke 2019;50:1380-1383.
18. Broderick JP, Brown RD, Jr., Sauerbeck L, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. Stroke 2009;40:1952-57.
19. Brown BM, Soldevilla F. MR angiography and surgery for unruptured familial intracranial aneurysms in persons with a family history of cerebral aneurysms. AJR Am J Roentgenol 1999;173:133-138.
20. Brown RD, Jr., Huston J, Hornung R, et al. Screening for brain aneurysm in the Familial Intracranial Aneurysm study: frequency and predictors of lesion detection. J Neurosurg 2008;108:1132-1138.
21. Chan DY, Abrigo JM, Cheung TC, et al. Screening for intracranial aneurysms? Prevalence of unruptured intracranial aneurysms in Hong Kong Chinese. J Neurosurg 2016;124:1245-1249.
22. Goksu E, Akyuz M, Tuncer R. The results of radiological screening in asymptomatic at-risk members of intracranial aneurysm families from the Turkish population. Turk Neurosurg 2012;22:55-61.
23. Kojima M, Nagasawa S, Lee YE, et al. Asymptomatic familial cerebral aneurysms. Neurosurgery 1998;43:776-781.
24. Leblanc R, Worsley KJ, Melanson D, et al. Angiographic screening and elective surgery of familial cerebral aneurysms: a decision analysis. Neurosurgery 1994;35:9-18; discussion 18-19.
25. Wang MC, Rubinstein D, Kindt GW, et al. Prevalence of intracranial aneurysms in first-degree relatives of patients with aneurysms. Neurosurg Focus 2002;13:e2.
26. Bor AS, Rinkel GJ, van Norden J, et al. Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid haemorrhage: a cohort study. Lancet Neurol 2014;13:385-392.
27. Ronkainen A, Miettinen H, Karkola K, et al. Risk of harboring an unruptured intracranial aneurysm. Stroke 1998;29:359-362.
28. Galassi W, Yuyangkate W, Paholthep P, et al. Prevalence of unruptured intracranial aneurysms among first-degree relatives of Thai patients who had aneurysmal subarachnoid hemorrhage. Surg Neurol Int 2021;12:566.
29. Agarwal N, Gala NB, Choudhry OJ, et al. Prevalence of asymptomatic incidental aneurysms: a review of 2,685 computed tomographic angiograms. World Neurosurg 2014;82:1086-1090.
30. Asaithambi G, Adil MM, Chaudhry SA, et al. Incidences of unruptured intracranial aneurysms and subarachnoid hemorrhage: results of a statewide study. J Vasc Interv Neurol 2014;7:14-17.
31. Bos D, Poels MM, Adams HH, et al. Prevalence, Clinical Management, and Natural Course of Incidental Findings on Brain MR Images: The Population-based Rotterdam Scan Study. Radiology 2016;281:507-515.
32. Harada K, Fukuyama K, Shirouzu T, et al. Prevalence of unruptured intracranial aneurysms in healthy asymptomatic Japanese adults: differences in gender and age. Acta Neurochir (Wien) 2013;155:2037-2043.
33. Horikoshi T, Akiyama I, Yamagata Z, et al. Retrospective analysis of the prevalence of asymptomatic cerebral aneurysm in 4518 patients undergoing magnetic resonance angiography--when does cerebral aneurysm develop? Neurol Med Chir (Tokyo) 2002;42:105-112; discussion 113.
34. Igase K, Matsubara I, Igase M, et al. Initial experience in evaluating the prevalence of unruptured intracranial aneurysms detected on 3-tesla MRI. Cerebrovasc Dis 2012;33:348-353.
35. Inagawa T, Hirano A. Autopsy study of unruptured incidental intracranial aneurysms. Surg Neurol 1990;34:361-365.
36. Jeon TY, Jeon P, Kim KH. Prevalence of unruptured intracranial aneurysm on MR angiography. Korean J Radiol 2011;12:547-553.
37. Kim JH, Lee KY, Ha SW, et al. Prevalence of Unruptured Intracranial Aneurysms: A Single Center Experience Using 3T Brain MR Angiography. Neurointervention 2021;16:117-121.
38. Kobayashi H, Tsuji T, Ishii H, et al. Diagnosis of unruptured asymptomatic cerebral aneurysms by magnetic resonance angiography. J Clin Neurosci 1997;4:197-200.
39. Li J, Shen B, Ma C, et al. 3D contrast enhancement-MR angiography for imaging of unruptured cerebral aneurysms: a hospital-based prevalence study. PLoS One 2014;9:e114157.
40. Li MH, Chen SW, Li YD, et al. Prevalence of unruptured cerebral aneurysms in Chinese adults aged 35 to 75 years: a cross-sectional study. Ann Intern Med 2013;159:514-521.
41. Müller TB, Sandvei MS, Kvistad KA, et al. Unruptured intracranial aneurysms in the Norwegian Nord-Trøndelag Health Study (HUNT): risk of rupture calculated from data in a population-based cohort study. Neurosurgery 2013;73:256-261.
42. Nakagawa T, Hashi K. The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. J Neurosurg 1994;80:217-223.
43. Thien A, See AA, Ang SY, et al. Prevalence of Asymptomatic Unruptured Intracranial Aneurysms in a Southeast Asian Population. World Neurosurg 2017;97:326-332.
44. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. N Engl J Med 2007;357:1821-1828.
45. Winn HR, Jane JA, Sr., Taylor J, et al. Prevalence of asymptomatic incidental aneurysms: review of 4568 arteriograms. J Neurosurg 2002;96:43-49.
46. Yue NC, Longstreth WT, Jr., Elster AD, et al. Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. Radiology 1997;202:41-46.
47. Ronkainen A, Hernesniemi J, Puranen M, et al. Familial intracranial aneurysms. Lancet 1997;349:380-384.
48. Iwamoto H, Kiyohara Y, Fujishima M, et al. Prevalence of intracranial saccular aneurysms in a Japanese community based on a consecutive autopsy series during a 30-year observation period. The Hisayama study. Stroke 1999;30:1390-1395.
49. Kapoor K, Kak VK. Incidence of intracranial aneurysms in north-west Indian population. Neurol India 2003;51:22-6.
50. Mostafazadeh B, Farzaneh Sheikh E, Afsharian Shishvan T, et al. The incidence of berry aneurysm in the Iranian population: an autopsy study. Turk Neurosurg 2008;18:228-31.
51. Thulung S, Aryal B, Baniya A, et al. Prevalence of Ruptured Intracranial Aneurysms in a Tertiary Care Hospital of Nepal. JNMA J Nepal Med Assoc 2019;57:168-171.
52. Bechstein M, Gansukh A, Regzengombo B, et al. Risk Factors for Cerebral Aneurysm Rupture in Mongolia. Clin Neuroradiol 2021;32:499-506.
53. Fukuhara T. Geographical analysis of aneurysmal subarachnoid hemorrhage in Japan utilizing publically-accessible DPC database. PLoS One 2015;10:e0122467.
54. Hamada J, Morioka M, Yano S, et al. Incidence and early prognosis of aneurysmal subarachnoid hemorrhage in Kumamoto Prefecture, Japan. Neurosurgery 2004;54:31-8.
55. Huang H, Lai LT. Incidence and Case-Fatality of Aneurysmal Subarachnoid Hemorrhage in Australia, 2008-2018. World Neurosurg 2020;144:e438-e446.
56. Inagawa T, Ishikawa S, Aoki H, et al. Aneurysmal subarachnoid hemorrhage in Izumo City and Shimane Prefecture of Japan. Incidence. Stroke 1988;19:170-175.
57. Keris V, Buks M, Macane I, et al. Aneurysmal subarachnoid hemorrhage in Baltic population: experience from Latvia (1996-2000). Eur J Neurol 2002;9:601-607.
58. Lee HS, Kim YJ, You SH, et al. The incidence of aneurysmal subarachnoid hemorrhage in youngdong district, Korea. J Korean Neurosurg Soc 2007;42:258-264.
59. Lee WK, Oh CW, Lee H, et al. Factors influencing the incidence and treatment of intracranial aneurysm and subarachnoid hemorrhage: time trends and socioeconomic disparities under an universal healthcare system. J Neurointerv Surg 2019;11:159-165.
60. Marks PV, Hope JK, Cluroe AD, et al. Racial differences between Maori and European New Zealanders in aneurysmal subarachnoid haemorrhage. Br J Neurosurg 1993;7:175-181.
61. Mathieu J, Pérusse L, Allard P, et al. Epidemiological study of reptured intracranial aneurysms in the Saguenay-Lac-Saint-Jean region (Quebec, Canada). Can J Neurol Sci 1996;23:184-188.
62. Nogueira GJ. Spontaneous subarachnoid haemorrhage and ruptured aneurysms in the Middle East. A myth revisited. Acta Neurochir (Wien) 1992;114:20-25.
63. Ohkuma H, Fujita S, Suzuki S. Incidence of aneurysmal subarachnoid hemorrhage in Shimokita, Japan, from 1989 to 1998. Stroke 2002;33:195-199.

References

64. Øie LR, Solheim O, Majewska P, et al. Incidence and case fatality of aneurysmal subarachnoid hemorrhage admitted to hospital between 2008 and 2014 in Norway. Acta Neurochir (Wien) 2020;162:2251-2259.
65. Oyoshi T, Nakayama M, Kuratsu J. Relationship between aneurysmal subarachnoid hemorrhage and climatic conditions in the subtropical region, Amami-Oshima, in Japan. Neurol Med Chir (Tokyo) 1999;39:585-90; discussion 590-591.
66. Rahmanian A, Jamali M, Bagheri Lankarani K, et al. Aneurysmal subarachnoid haemorrhage (aSAH): Five consecutive years' experience of Fars province, Iran. PLoS One 2017;12:e0189005.
67. Roessler K, Cejna M, Zachenhofer I. Aneurysmatic subarachnoidal haemorrhage: incidence and location of small ruptured cerebral aneurysms - a retrospective population-based study. Wien Klin Wochenschr 2011;123:444-449.
68. Sandvei MS, Mathiesen EB, Vatten LJ, et al. Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts, 1984-2007. Neurology 2011;77:1833-1839.
69. Sandvei MS, Romundstad PR, Müller TB, et al. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. Stroke 2009;40:1958-1962.
70. Schatlo B, Fung C, Stienen MN, et al. Incidence and Outcome of Aneurysmal Subarachnoid Hemorrhage: The Swiss Study on Subarachnoid Hemorrhage (Swiss SOS). Stroke 2021;52:344-347.
71. Tamasauskas A, Tamasauskas J, Bernotas G, et al. Management of patients with ruptured cerebral aneurysms in hospital population of Lithuania. Acta Neurochir (Wien) 2000;142:51-59.
72. Ziemba-Davis M, Bohnstedt BN, Payner TD, et al. Incidence, epidemiology, and treatment of aneurysmal subarachnoid hemorrhage in 12 midwest communities. J Stroke Cerebrovasc Dis 2014;23:1073-1082.
73. Lee SU, Kim T, Kwon OK, et al. Trends in the Incidence and Treatment of Cerebrovascular Diseases in Korea : Part I. Intracranial Aneurysm, Intracerebral Hemorrhage, and Arteriovenous Malformation. J Korean Neurosurg Soc 2020;63:56-68.
74. Majewska P, Gulati S, Øie L, et al. Smoking habits and detection rate of unruptured intracranial aneurysms and incidence rate of subarachnoid haemorrhage in Norway between 2008 and 2015. Acta Neurochir (Wien) 2020;162:3161-3165.
75. Gabriel RA, Kim H, Sidney S, et al. Ten-year detection rate of brain arteriovenous malformations in a large, multiethnic, defined population. Stroke 2010;41:21-26.
76. Kim T, Lee H, Ahn S, et al. Incidence and risk factors of intracranial aneurysm: A national cohort study in Korea. Int J Stroke 2016;11:917-927.
77. Menghini VV, Brown RD, Jr., Sicks JD, et al. Incidence and prevalence of intracranial aneurysms and hemorrhage in Olmsted County, Minnesota, 1965 to 1995. Neurology 1998;51:405-411.
78. Raja IA, Javaid MA. Aneurysm surgery in Pakistan. Neurol Med Chir (Tokyo) 1998;38 Suppl:134-137.
79. Park S, Lee DH, Ryu CW, et al. Incidental Saccular Aneurysms on Head MR Angiography: 5 Years' Experience at a Single Large-Volume Center. J Stroke 2014;16:189-194.
80. Isaksen J, Egge A, Waterloo K, et al. Risk factors for aneurysmal subarachnoid haemorrhage: the Tromsø study. J Neurol Neurosurg Psychiatry 2002;73:185-187.
81. Inagawa T. Trends in incidence and case fatality rates of aneurysmal subarachnoid hemorrhage in Izumo City, Japan, between 1980-1989 and 1990-1998. Stroke 2001;32:1499-1507.
82. Lee LS, Huang SL. Aneurysmal subarachnoid hemorrhage in Taiwan. Neurol Med Chir (Tokyo) 1998;38 Suppl:122-123.
83. Backes D, Rinkel GJ, Algra A, et al. Increased incidence of subarachnoid hemorrhage during cold temperatures and influenza epidemics. J Neurosurg 2016;125:737-745.
84. Worldometer. U.K. Population. Volume 2022, 2021. https://www.worldometers.info/. Accessed 15/02/2022.
85. Kim DH, Van Ginhoven G, Milewicz DM. Incidence of familial intracranial aneurysms in 200 patients: comparison among Caucasian, African-American, and Hispanic populations. Neurosurgery 2003;53:302-308.
86. Schievink WI, Schaid DJ, Michels VV, et al. Familial aneurysmal subarachnoid hemorrhage: a community-based study. J Neurosurg 1995;83:426-429.
87. Mathieu J, Hébert G, Pérusse L, et al. Familial intracranial aneurysms: recurrence risk and accidental aggregation study. Can J Neurol Sci 1997;24:326-331.
88. Ishibashi T, Murayama Y, Urashima M, et al. Unruptured intracranial aneurysms: incidence of rupture and risk factors. Stroke 2009;40:313-316.
89. Slot EMH, Rinkel GJE, Algra A, et al. Patient and aneurysm characteristics in familial intracranial aneurysms. A systematic review and meta-analysis. PLoS One 2019;14:e0213372.
90. ACROSS. Epidemiology of aneurysmal subarachnoid hemorrhage in Australia and New Zealand: incidence and case fatality from the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). Stroke 2000;31:1843-1850.
91. Lin N, Cahill KS, Frerichs KU, et al. Treatment of ruptured and unruptured cerebral aneurysms in the USA: a paradigm shift. J Neurointerv Surg 2012;4:182-189.
92. Akagawa H, Narita A, Yamada H, et al. Systematic screening of lysyl oxidase-like (LOXL) family genes demonstrates that LOXL2 is a susceptibility gene to intracranial aneurysms. Hum Genet 2007;121:377-387.
93. Berthelemy-Okazaki N, Zhao Y, Yang Z, et al. Examination of ELN as a candidate gene in the Utah intracranial aneurysm pedigrees. Stroke 2005;36:1283-1284.
94. Bourcier R, Le Scouarnec S, Bonnaud S, et al. Rare Coding Variants in ANGPTL6 Are Associated with Familial Forms of Intracranial Aneurysm. Am J Hum Genet 2018;102:133-141.
95. Deka R, Koller DL, Lai D, et al. The relationship between smoking and replicated sequence variants on chromosomes 8 and 9 with familial intracranial aneurysm. Stroke 2010;41:1132-1137.
96. Ding X, Zhao S, Zhang Q, et al. Exome sequencing reveals a novel variant in NFX1 causing intracranial aneurysm in a Chinese family. J Neurointerv Surg 2020;12:221-226.
97. Farlow JL, Lin H, Sauerbeck L, et al. Lessons learned from whole exome sequencing in multiplex families affected by a complex genetic disorder, intracranial aneurysm. PLoS One 2015;10:e0121104.
98. Farnham JM, Camp NJ, Neuhausen SL, et al. Confirmation of chromosome 7q11 locus for predisposition to intracranial aneurysm. Hum Genet 2004;114:250-255.
99. Foroud T, Koller DL, Lai D, et al. Genome-wide association study of intracranial aneurysms confirms role of Anril and SOX17 in disease risk. Stroke 2012;43:2846-2852.
100. Foroud T, Sauerbeck L, Brown R, et al. Genome screen in familial intracranial aneurysm. BMC Med Genet 2009;10:3.
101. Foroud T, Sauerbeck L, Brown R, et al. Genome screen to detect linkage to intracranial aneurysm susceptibility genes: the Familial Intracranial Aneurysm (FIA) study. Stroke 2008;39:1434-1440.
102. Hashikata H, Liu W, Inoue K, et al. Confirmation of an association of single-nucleotide polymorphism rs1333040 on 9p21 with familial and sporadic intracranial aneurysms in Japanese patients. Stroke 2010;41:1138-1144.
103. Hirota K, Akagawa H, Onda H, et al. Association of rare nonsynonymous variants in PKD1 and PKD2 with familial intracranial aneurysms in a Japanese population. Journal of Stroke and Cerebrovascular Diseases. 2016;25:2900-2906.
104. Hofer A, Hermans M, Kubassek N, et al. Elastin polymorphism haplotype and intracranial aneurysms are not associated in Central Europe. Stroke 2003;34:1207-1211.
105. Hofer A, Ozkan S, Hermans M, et al. Mutations in the lysyl oxidase gene not associated with intracranial aneurysm in central European families. Cerebrovasc Dis 2004;18:189-193.
106. Hostettler IC, O'Callaghan B, Bugiardini E, et al. ANGPTL6 genetic variants are an underlying cause of familial intracranial aneurysms. Neurology 2021 ;96:e947-955.
107. Kim CJ, Park SS, Lee HS, et al. Identification of an autosomal dominant locus for intracranial aneurysm through a model-based family collection in a geographically limited area. J Hum Genet 2011;56:464-466.
108. Krischek B, Narita A, Akagawa H, et al. Is there any evidence for linkage on chromosome 17cen in affected Japanese sib-pairs with an intracranial aneurysm? J Hum Genet 2006;51:491-494.
109. Li M, Dong X, Chen S, et al. Genetic polymorphisms and transcription profiles associated with intracranial aneurysm: a key role for NOTCH3. Aging (Albany NY) 2019;11:5173-5191.
110. Lorenzo-Betancor O, Blackburn PR, Edwards E, et al. PCNT point mutations and familial intracranial aneurysms. Neurology 2018;91:e2170-e2181.
111. Mineharu Y, Inoue K, Inoue S, et al. Model-based linkage analyses confirm chromosome 19q13.3 as a susceptibility locus for intracranial aneurysm. Stroke 2007;38:1174-8.
112. Roberts GA, Corcoran BT, Pfouts LL, et al. Genetic evaluation of lipoprotein(a) in intracranial aneurysm disease. Neurosurgery 2001;49:133-142.
113. Roos YB, Pals G, Struycken PM, et al. Genome-wide linkage in a large Dutch consanguineous family maps a locus for intracranial aneurysms to chromosome 2p13. Stroke 2004;35:2276-2281.
114. Ruigrok YM, Wijmenga C, Rinkel GJ, et al. Genomewide linkage in a large Dutch family with intracranial aneurysms: replication of 2 loci for intracranial aneurysms to chromosome 1p36.11-p36.13 and Xp22.2-p22.32. Stroke 2008;39:1096-1102.
115. Santiago-Sim T, Depalma SR, Ju KL, et al. Genomewide linkage in a large Caucasian family maps a new locus for intracranial aneurysms to chromosome 13q. Stroke 2009;40:S57-60.
116. Santiago-Sim T, Fang X, Hennessy ML, et al. THSD1 (Thrombospondin Type 1 Domain Containing Protein 1) Mutation in the Pathogenesis of Intracranial Aneurysm and Subarachnoid Hemorrhage. Stroke 2016;47:3005-3013.
117. Santiago-Sim T, Mathew-Joseph S, Pannu H, et al. Sequencing of TGF-beta pathway genes in familial cases of intracranial aneurysm. Stroke 2009;40:1604-1611.
118. Sauvigny T, Alawi M, Krause L, et al. Exome sequencing in 38 patients with intracranial aneurysms and subarachnoid hemorrhage. Journal of neurology 2020;267:2533-2545.
119. van der Voet M, Olson JM, Kuivaniemi H, et al. Intracranial aneurysms in Finnish families: confirmation of linkage and refinement of the interval to chromosome 19q13.3. Am J Hum Genet 2004;74:564-5671.
120. Wu Y, Li Z, Shi Y, et al. Exome Sequencing Identifies LOXL2 Mutation as a Cause of Familial Intracranial Aneurysm. World Neurosurg 2018;109:e812-e818.
121. Yamada S, Utsunomiya M, Inoue K, et al. Genome-wide scan for Japanese familial intracranial aneurysms: linkage to several chromosomal regions. Circulation 2004;110:3727-3733.
122. Yamada S, Utsunomiya M, Inoue K, et al. Absence of linkage of familial intracranial aneurysms to 7q11 in highly aggregated Japanese families. Stroke 2003;34:892-900.
123. Yan J, Hitomi T, Takenaka K, et al. Genetic study of intracranial aneurysms. Stroke 2015;46:620-626.
124. Yang, X., Li, J., Fang, Y., Zhang, et al. Rho guanine nucleotide exchange factor ARHGEF17 is a risk gene for intracranial aneurysms. Circulation: Genomic and Precision Medicine 2018;11:p.e002099.

References

125. Yoneyama T, Kasuya H, Onda H, et al. Association of positional and functional candidate genes FGF1, FBN2, and LOX on 5q31 with intracranial aneurysm. J Hum Genet 2003;48:309-314.
126. Zhou S, Ambalavanan A, Rochefort D, et al. RNF213 Is Associated with Intracranial Aneurysms in the French-Canadian Population. Am J Hum Genet 2016;99:1072-1085.
127. Jourdan-Le Saux C, Le Saux O, Donlon T, et al. The human lysyl oxidase-related gene (LOXL2) maps between markers D8S280 and D8S278 on chromosome 8p21. 2–p21. 3. Genomics 1998;51:305-307.
128. National Center for Biotechnology Information. ARHGEF17 Rho guanine nucleotide exchange factor 17 - NIH Genetic Testing Registry (GTR), 2022. https://www.ncbi.nlm.nih.gov/gtr/genes/9828/. Accessed 26/07/2022.
129. MedlinePlus. NOTCH3 gene. National Library of Medicine, 2016. https://medlineplus.gov/genetics/gene/notch3/. Accessed 20/03/2022.
130. The Human Protein Atlas. ANGPTL6 protein expression summary. https://www.proteinatlas.org/ENSG00000130812-ANGPTL6. Accessed 26/07/2022.
131. Bush WS, Moore JH. Chapter 11: Genome-wide association studies. PLoS computational biology 2012;8:e1002822.
132. Yasuno K, Bakırcıoğlu M, Low S-K, et al. Common variant near the endothelin receptor type A (EDNRA) gene is associated with intracranial aneurysm risk. Proceedings of the National Academy of Sciences 2011;108:19707-19712.
133. Yasuno K, Bilguvar K, Bijlenga P, et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. Nature genetics 2010;42:420-425.
134. National Institute for Health and Care Excellence. Subarachnoid haemorrhage [T] Evidence review for investigating relatives of people with aneurysmal SAH, 2021. https://www.nice.org.uk/guidance/GID-NG10097/documents/evidence-review-3. Accessed 07/12/2022.
135. Ledbetter LN, Burns J, Shih RY, et al. ACR Appropriateness Criteria® Cerebrovascular Diseases-Aneurysm, Vascular Malformation, and Subarachnoid Hemorrhage. Journal of the American College of Radiology 2021;18:S283-S304.
136. Cho W-S, Kim JE, Park SQ, et al. Korean clinical practice guidelines for aneurysmal subarachnoid hemorrhage. Journal of Korean Neurosurgical Society 2018;61:127.
137. AIM Specialty Health. Clinical Appropriateness Guidelines: Advanced Imaging, 2018. https://aimspecialtyhealth.com/guidelines/PDFs/2018/Jan01/AIM_Guidelines.pdf. Accessed 10/12/2022.
138. Thompson BG, Brown Jr RD, Amin-Hanjani S, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:2368-2400.
139. Jeong HW, Seo JH, Kim ST, et al. Clinical practice guideline for the management of intracranial aneurysms. Neurointervention 2014;9:63.
140. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovascular diseases 2013;35:93-112.
141. Connolly Jr ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012;43:1711-1737.
142. Hayes LL, Palasis S, Bartel TB, et al. ACR appropriateness criteria® Headache–child. Journal of the American College of Radiology 2018;15:S78-S90.
143. ter Berg H, Dippel D, Limburg M, et al. Familial intracranial aneurysms. A review. Stroke 1992;23:1024-1030.

HBA Support

hbasupport.org

Company number: 13428276

costello medical

HBA Support would like to thank Costello Medical who conducted the TLR and supported the development of this report on a pro bono basis.