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INTRACRANIAL ANEURYSMS – FAMILIAL AND HEREDITARY PREDISPOSITION IN EASTERN FINLAND

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ABSTRACT

Intracranial aneurysms (IA), whether saccular (sIA) or, rarely, fusiform (fIA), can lead to rupture with devastating sequalae. The Kuopio IA Patient and Family Database contains all cases of unruptured sIAs and fIAs, and patients with aneurysmal subarachnoid haemorrhage (aSAH) were admitted to the Kuopio University Hospital from its defined catchment population. Data from several national registries, including the hospital diagnosis registry, medicine reimbursement statistics and the population register have been integrated to the database. The population register has been used to obtain corresponding information on the first-degree relatives of the patients and to create a matched control population to the patients.

This doctoral thesis study had three aims. The first was to determine the prevalence of neurofibromatosis type 1 (NF), a monogenic disorder, in the population-based cohort of IA and aSAH patients, as well as the diagnoses of IA and aSAH in a reverse approach in a nationwide database of NF1 patients. The second aim was to identify families in which parents were concordant for sIA disease, study the propagation of sIA disease to their children, and to study the effect of the familial versus sporadic sIA disease on the sIA risk of the offspring. Thirdly, the study aimed to determine the frequency of abdominal aortic aneurysms (AAA) and thoracic aortic aneurysms (TAA) in sIA and fIA patients and to evaluate a possible genetic connection between fIA and aortic aneurysms.

Only one NF1 patient was identified among the 4,543 IA patients, in line with the prevalence of NF1 in the general population (1/4,500). Three verified IA cases (one unruptured IA and two aSAH cases) were identified in the cohort of 1,410 NF1 patients, with an occurrence of similar magnitude in the control cohort.

A total of 18 couples concordant for the sIA disease with a total of 48 children were identified. Six sporadic-sporadic couples were concordant for subarachnoid haemorrhage (SAH). None of the 24 children to the 12 sporadic-sporadic couples had been diagnosed with SAH or IA disease. Instead, 11 (46%) of the 24 children to the 6 familial-sporadic couples had been diagnosed with SAH or IA disease.

The proportion of fIA diagnosed with AA was 14%. In comparison, 1.2% of sIA patients had a diagnosis of AA. Both fIA and sIA patients had AAs significantly more often than their (1.2% and 0.5%) controls or relatives (0.9% and 0.3%). One likely pathogenic variant in *COL5A2* and three variants of unknown significance were identified in *MYH11*, *COL11A1*, and *FBN1* in four fIA patients.

The results of this doctoral thesis clarify the contested relationship of intracranial aneurysms and NF1, underline the importance of looking at the family history of a patient presenting with an intracranial aneurysm or aneurysmal subarachnoid haemorrhage and provide the impetus to consider screening all patients with fusiform IA for aortic aneurysms.

Keywords: intracranial aneurysm; subarachnoid haemorrhage; aortic aneurysm, abdominal; aortic aneurysm, thoracic; neurofibromatosis 1; genetics, epidemiology

Kurtelius Arttu
Aivovaltimoaneurysmataudin familiaaliset ja perinnölliset altisteet itäsuomalaisessa väestössä
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TIIVISTELMÄ

Kallonsisäiset aivovaltimoaneurysmat voivat olla muodoltaan sakkulaarisia (sIA) tai fusiformisia (fIA). Kallonsisäisten aivovaltimoaneurysmien olennaisena riskinä on aneurysman puhkeamiseen liittyvä, taudinkuvaltaan vaikea aivoverenkiertohäiriö, subaraknoidaalivuoto. Kuopion aneurysmatietokanta, johon tämä väitöstutkimus perustuu, muodostuu kaikista Kuopion yliopistolliseen sairaalaan puhkeamattoman aivovaltimoaneurysman tai aneurysmaattisen subaraknoidaalivuodon takia hoitoon otetuista potilaista. Aneurysmarekisteriin on yhdistetty kansallisten hoitoilmoitusrekisterin ja lääkekorvausrekisterin sekä väestörekisterin tiedot. Väestörekisterin avulla on tunnistettu rekisterin aneurysmapotilaiden ensimmäisen asteen sukulaiset, joista rekisterissä on vastaavat tiedot, sekä muodostettu kaltaistettu verrokkiaineisto.

Tällä väitöstutkimuksella oli kolme tavoitetta: määrittää tyypin 1 neurofibromatoosin (NF1) yleisyys Kuopion aneurysmarekisterin väestöpohjaisessa potilaskohortissa ja toisaalta aivovaltimoaneurysma- ja subaraknoidaalivuotodiagnoosien ilmaantuvuus kansallisessa NF1-tietokannassa; tunnistaa aneurysmatietokannasta perheet, joiden molemmat vanhemmat ovat aivovaltimoaneurysmataudin kantajia ja tutkia taudin periytymistä näissä perheissä ja selvittää taudin familiaalisen ja sporadisen muodon vaikutusta tähän periytymiseen; määrittää vatsa- ja rinta-aortan aneurysmien yleisyys aneurysmatietokannan sIA- ja fIA-potilaiden joukossa ja tutkia fusiformisten aivovaltimoaneurysmien ja aortan aneurysmien välistä mahdollista geneettistä yhteyttä.

Vain yhdellä aneurysmatietokannan 4543 potilaasta oli diagnosoitu NF1, mikä vastaa NF1:n esiintyvyyttä suomalaisessa väestössä (1/4500). Kolmella NF1-rekisterin potilaalla oli varmistettu aivovaltimoaneurysma- tai subaraknoidaalivuotodiagnoosi. Diagnoosien ilmaantuvuus ei ollut merkitsevästi vähäisempi NF1-rekisterin kontrollipotilaskohortissa.

Aneurysmarekisteristä tunnistetiin 18 perhettä, joissa molemmat vanhemmat olivat aneurysmataudin kantajia. Kuudessa perheessä toisella vanhemmista oli familiaalinen tauti ja 12:ssa molempien vanhempien tauti oli sporadinen. Yhdelläkään jälkimmäisen ryhmän perheiden 24 lapsesta ei ollut diagnosoitua aivovaltimoaneurysmatautia. Kuudessa perheessä, joissa toisella vanhemmista oli familiaalinen tauti, oli yhteensä 24 lapsesta 11:llä (46 %) diagnosoitu aneurysmatauti.

Aneurysmarekisterin 125 potilaasta, joilla oli diagnosoitu fusiforminen aivovaltimoaneurysma, 17:llä (14 %) oli diagnosoitu myös aortan aneurysma. Vastaavasti 1,2 % potilaista, joilla oli sakkulaarinen aivovaltimoaneurysma, oli myös diagnosoitu aortan aneurysma. Molemmissa potilasryhmissä oli aortan aneurysmien yleisyys merkitsevästi yleisempi kuin verrokkiaineistossa tai potilaiden ensimmäisen asteen sukulaisten joukossa. Yhdellä fIA-potilaalla todettiin todennäköisesti patogeneettinen mutaatio *COL5A2*-geenissä. Lisäksi kolmella potilaalla todettiin merkitykseltään epäselvä geenivariantti *MYH11-*, *COL11A1-* ja *FBN1*-geeneissä.

Yhteenvetona voidaan todeta, että väitöskirja selventää NF1:n ja aivovaltimoaneurysmien epäselvää yhteyttä, korostaa sukuanamneesin merkitystä aivovaltimoaneurysmapotilaan arvioimisessa ja antaa aiheen harkita kaikkien fIA-potilaiden seulomista aortan aneurysmien varalta.

Avainsanat: aneurysma, kallonsisäinen aneurysma, vatsa-aortan aneurysma, aivoverenvuoto, neurofibromatoosi 1, perinnöllisyystiede, epidemiologia

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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Kurtelius A, Kallionpää RA, Huttunen J, Huttunen TJ, Helin K, Koivisto T, Frösen J, von Und Zu Fraunberg M, Peltonen S, Peltonen J, Jääskeläinen JE, Lindgren AE. Neurofibromatosis type 1 is not associated with subarachnoid haemorrhage. PLoS One. 2017;12(6):e0178711

II Kurtelius A, Kurki MI, von und zu Fraunberg M, Väntti N, Kotikoski S, Nurmonen H, Koivisto T, Jääskeläinen JE, Lindgren AE. Saccular intracranial aneurysms in children when both parents are sporadic or familial carriers of saccular intracranial aneurysms. Neuroepidemiology. 2018;52(1–2):47–54

III Kurtelius A, Vänttinen N, Jahromi BR, Tähtinen O, Manninen H, Koskenvuo J, Tulamo R, Kotikoski S, Nurmonen H, Kämäräinen OP, Huttunen T, Hututnen J, von und zu Fraunberg M, Koivisto T, Jääskeläinen JE, Lindgren AE. Association of intracranial aneurysms with aortic aneurysms in 125 patients with fusiform and 4,253 patients with saccular intracranial aneurysms and their family members and population controls. JAHA. 2019;8(18):e013277

CONTENTS

ABBREVIATIONS

AA	Aortic aneurysm
AAA	Abdominal aortic aneurysm
ACA	Anterior cerebral artery
ACE	Angiotensin-converting enzyme
ACoA	Anterior communicating artery
ADHD	Attention deficit hyperactivity syndrome
ADPKD	Autosomal dominant polycystic kidney disease
AICA	Anterior inferior cerebellar artery
ASA	Acetylsalicylic acid
aSAH	Aneurysmal subarachnoid haemorrhage
ARB	Angiotensin receptor blocker
BA	Basilar artery
BAV	Bicuspid aortic valve
CI	Confidence interval
CoA	Coarctation of the aorta
CT	Computed tomography
CTA	Computed tomography angiography
DSA	Digital subtraction angiography
ECM	Extracellular matrix
EVAR	Endovascular aortic repair
fIA	Fusiform intracranial aneurysm
gnomAD	Genome Aggregation Database
GWAS	Genome-wide association study
HGMD	Human Gene Mutation Database
HR	Hazard ratio
HT	Hypertension
IA	Intracranial aneurysm
IADE	Intracranial dolichoectasia
ICA	Internal carotid artery
ICH	Intracerebral haemorrhage
IEL	Internal elastic lamina
MAF	Minor allele frequency
MCA	Middle cerebral artery

MEK	Mitogen-activated protein kinase kinase
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
NF1	Neurofibromatosis type 1
NF2	Neurofibromatosis type 2
OR	Odds ratio
PCoA	Posterior communicating artery
PDGFRB	Platelet-derived growth factor receptor β
PICA	Posterior inferior cerebellar artery
SAH	Subarachnoid haemorrhage
SCA	Superior cerebellar artery
sIA	Saccular intracranial aneurysm
SMC	Smooth muscle cell
TAA	Thoracic aortic aneurysm
TEE	Transoesophageal echocardiography
TGF-β	Transforming growth factor β
TTE	Transthoracic echocardiography
UBO	Unidentified bright objects

1 INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH), typically caused by a rupture of a saccular aneurysm on an intracranial extracerebral artery, is the third most common form of stroke after brain infarction and intracerebral haemorrhage.[6,7] Intracranial and other aneurysms can be dichotomised to saccular and fusiform aneurysms based on their shape. In comparison to saccular intracranial aneurysms (sIA), fusiform intracranial aneurysms (fIA) are rare and remain poorly characterised as a disease entity. In contrast to the sIA disease, fIAs often present with nonhaemorrhagic complications.[8]

The risk of developing saccular IA is affected by both environmental and familial, genomic, epigenomic and genetic factors. Traditional risk factors include age, female gender, smoking and hypertension.[9] Autosomal dominant polycystic kidney disease (ADPKD), despite its rarity (1%) among sIA patients, is notable for its significant and well-characterised association with the sIA disease.[10,11] Like many other complex diseases and traits, IA often aggregates in families, and approximately 10–20% of sIA patients belong to an sIA family.[9,12-15] The currently known genomic variants account for only a fraction of the observed sIA heritability, however.[16]

The risk for many of the complex diseases is increased markedly in children when both parents are carriers of the disease: examples of this phenomenon include hypertension[17] and both type 1[18] and type 2 diabetes.[19] The estimated general prevalence of sIA disease is some 3%:[20] consequently, couples in which both spouses are sIA patients, or will be later in their lives, should be uncommon but not exceedingly so (up to 9/1,000) in the general population. It is not known whether children born to parents concordant for intracranial aneurysm disease are at increased risk of sIA disease or aSAH.

Neurofibromatosis type 1 (NF1) is a relatively common autosomal dominant neurocutaneous disorder. The classical and diagnostic manifestations of NF1 include café-au-lait spots and neurofibromas of the skin and iris hamartomas.[21] NF1 is a multisystem disease characterised by diverse manifestations in different organ systems.[22,23] NF1 has been linked to different cardiovascular complications including renal artery stenosis, moyamoya disease and intracranial aneurysms.[23-27] The relationship between NF1 and intracranial aneurysms, however, is contentious.[26,28-30]

Unlike fIAs, fusiform aortic aneurysms (AA) are common in the aging population.[31-33] Family history is a risk factor for both thoracic aortic aneurysms (TAA) and abdominal aortic aneurysms (AAA).[31-33] The increased prevalence of intracranial aneurysms in patients with aortic aneurysms – as well as a reverse association – has been reported in several retrospective studies.[34-41] The published patient series have not been drawn from a defined catchment population, nor have the patients been assigned controls. Some cohorts have reported a high prevalence

of aortic aneurysms in patients with fIA, but no comparisons between fusiform and saccular IA patients have been made.

The Kuopio Intracranial Aneurysm Patient and Family Database (www.kuopioneurosurgery.fi) contains all cases of unruptured and ruptured sIAs admitted to the Kuopio University Hospital (KUH) from a defined Eastern Finnish catchment population. Clinical data for the sIA patients and their relatives have been obtained from the national registries. We have studied the phenotype,[13] long-term outcome,[13,42-46] concomitant diseases (e.g., hypertension,[47,48] diabetes[49] and ADPKD[10]) and genomics[16] of both sporadic and familial forms of the sIA disease. The goal of the present study is to assess the segregation of intracranial aneurysm disease and its association with other complex and monogenic diseases such as aortic aneurysm disease and neurofibromatosis type 1. This advances the individualised risk prediction and development of diagnostic, preventive and follow-up tools and protocols for patients at risk for aneurysmal disease.

2 REVIEW OF THE LITERATURE

2.1 SACCULAR INTRACRANIAL ANEURYSMS

Intracranial saccular aneurysms are pouch-like dilatations of large intracranial arteries. They usually develop after the age of 40, and they may rupture, causing a haemorrhage into the subarachnoid space and sometimes into the brain tissue and brain ventricles.[9,50]

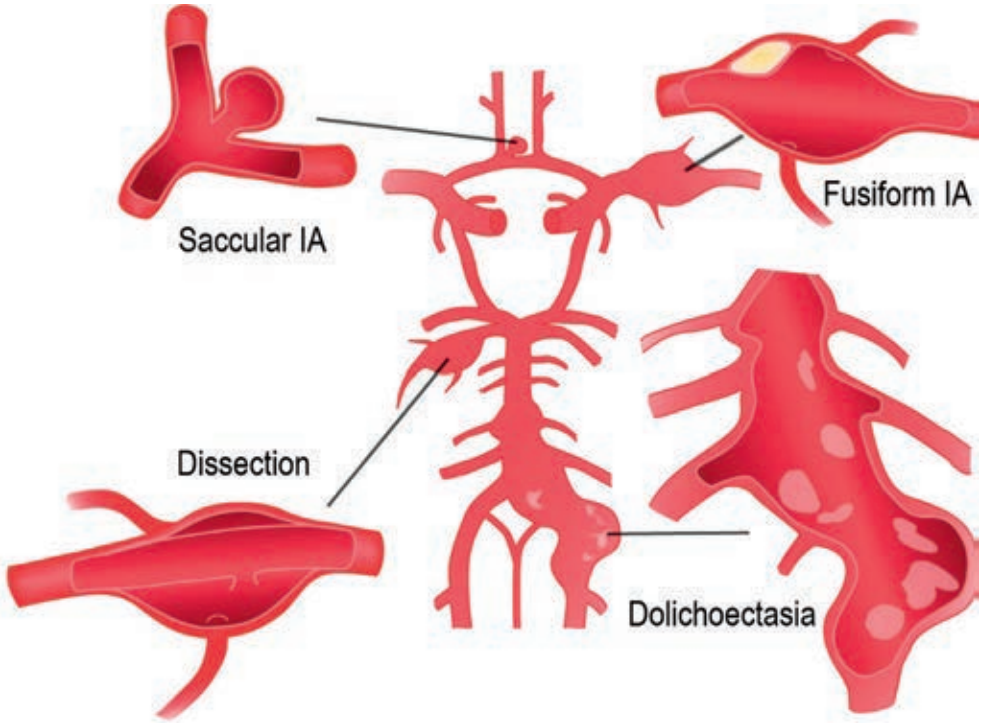

Figure 1 The major intracranial extracerebral arteries with the circle of Willis (middle). The saccular intracranial aneurysm (sIA, left upper) forms at the branching sites of the arteries, whereas the uncommon fusiform intracranial aneurysm (fIA, right upper) mainly involves the arterial trunks. Dolichoectasia (right lower) usually involves the vertebrobasilar trunk. Acute dissection with false lumen (left lower), more frequent in the cervical arteries, is also shown. Note the atheromatous plaque of the fIA wall and the calcification of the dolichoectatic artery. Reprinted from Kurtelius et al.[344]

2.1.1 Epidemiology of saccular intracranial aneurysms

Unruptured intracranial saccular aneurysms are relatively common. As unruptured sIAs are usually asymptomatic,[20] their true frequency in the population is hardly ascertainable. The exact prevalence estimates vary considerably between different cohorts, and the presence of different defined risk factors such as family history affect the reported prevalence of the disease.[20] A large systematic review of 68 studies and a meta-analysis of 31 from 1955 to 2011 report a prevalence estimate of 3.2% in a population without specific comorbidities, a mean age of 50 years and equal gender distribution.[20]

2.1.2 Aneurysmal subarachnoid haemorrhage (aSAH)

The prevalence of unruptured sIAs and the incidence of aneurysmal subarachnoid haemorrhage are discordant. In contrast to the relative commonness of UIAs (annual prevalence some 3000 per 100 000), aneurysm rupture remains a relatively rare event at an estimated annual global incidence of 7.9 per 100 000.[6] The incidence of aSAH with regional differences has declined significantly during the last few decades, probably driven by the declining smoking rate, the monitoring of blood pressure and effective treatment of hypertension.[6] The prevalence of aSAH has been traditionally reported to be approximately 20 per 100 000 person-years in Japan and Finland, twice the estimated global incidence.[51] However, the standardised incidence of aSAH has been considerably lower, at 7.4–8.9 per 100 000 person-years in the most recent studies.[52,53] In 2012, for example, there were 337 cases of aSAH in Finland as opposed to 510 in 1998.[52] The reasons for the previous, significantly larger incidence estimates may have been at least partly methodological. Regional differences exist in the incidence of hospital-admitted aSAH,[53] and several studies on the aSAH rate in Finland have investigated only a subset of the Finnish population.[52,53] Furthermore, due to a substantial proportion of cases presenting with sudden death, the autopsy rate – which has been relatively high in Finland – may have influenced the estimates.[52]

Subarachnoid haemorrhage remains a significant cause of mortality and morbidity compared to the two more frequent forms of stroke (brain infarction and intracerebral haemorrhage) and affects a disproportionately high percentage of working-age population. Approximately 10–20% patients die prior to reaching the hospital,[54,55] and total mortality has been estimated to reach 50%,[56] even though declining case fatality has been reported.[57,58] In an Eastern Finnish cohort, the 12-month mortality of hospitalised patients was 27%.[42] The long-term survivors of aSAH are characterised by excess mortality and neurologic morbidity, with approximately 20% of survivors remaining dependent and a considerable proportion of the rest suffering from different long-term sequalae.[59,60] In addition to neurocognitive dysfunction and focal neurologic deficits, shunt-dependent hydrocephalus and epilepsy are common neurological complications.[43,44] Psychiatric and

neuropsychiatric complications such as major depression and sleep disturbances occur frequently as well.[45,60]

2.1.3 Aetiology and pathophysiology of saccular intracranial aneurysms

Saccular intracranial aneurysms are acquired lesions. Although intracranial aneurysms and aSAH are occasionally encountered in paediatric patients,[61] aneurysms rarely develop before the second decade of life and are usually formed between the fourth and sixth decades.[20] Saccular intracranial arteries are typically formed in the branches or in the vicinity of the circle of Willis. Anatomical variations of the arterial pentagon may affect the risk of aneurysm formation: sharp angles and bifurcations involving hypoplastic arteries appear to increase the risk of sIA formation.[62] Interestingly, the medial raphe, a discontinuum in the smooth muscle cells of the media found in the bifurcations of cerebral arteries,[63] is more prominent in bifurcations with acute angles.[64] The role of the medial raphe in the formation of aneurysms, however, is unclear.[65,66]

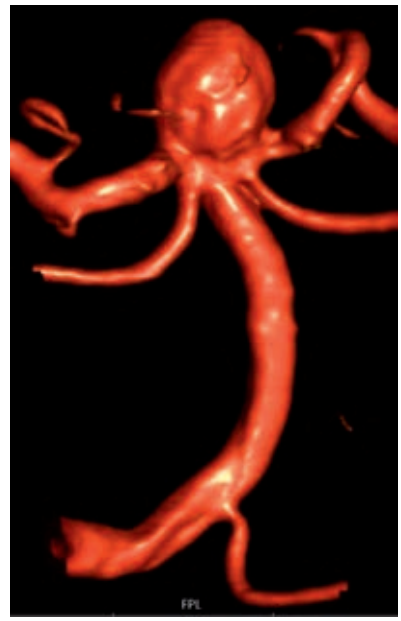

Figure 2 Saccular intracranial aneurysm at the tip of the basilar artery.

Known risk factors for sIA include both modifiable factors and non-modifiable characteristics. At the population level, age, sex, and family history are the most important non-modifiable risk factors. Saccular IAs occur only rarely before the age of 20, and both the incidence of unruptured sIA and aSAH increase with advancing age.[6,20,51,67] Although saccular IAs are more common in women of all ages, the excess of women is mainly explained by the increasing difference in IA prevalence after the age of 50.[20] The risk of aSAH is likewise increased in postmenopausal women.[6,7,68] The mechanism driving sex difference is not entirely clear. The results from studies investigating the effect of hormone replacement therapy,[68,69] oral contraceptives[68] and the reproductive cycle phase[68] are contradictory and do not provide a clear model for the effect that hormonal changes have on the risk of sIA formation and rupture.

Monogenic diseases such as autosomal dominant polycystic kidney disease (ADPKD) can significantly increase the risk of sIA at the individual and family levels.[11,70] The association of sIA and several connective tissue disorders such as Marfan syndrome, vascular Ehlers-Danlos syndrome and Loeys-Dietz syndrome has been proposed; the prevalence estimates of intracranial aneurysms in these patient populations vary considerably, and no prospective screening studies have been

performed.[29,71-73] Case reports of atypical presentations in conjunction with these syndromes are numerous.[74-76] Only a fraction of the total number of sIAs can be explained by monogenic diseases, however.[77]

Smoking and hypertension are the principal acquired risk factors for sIA formation and rupture. The prevalence of hypertension, is high (up to 70%) among patients with unruptured sIA.[47] There is a two- to threefold increase in the risk of aSAH due to hypertension.[78] The risk of aSAH increases gradually by increasing blood pressure: in a pooled analysis of prospective cohorts, an increase of 10 millimetres of mercury in systolic blood pressure is associated with a 30% difference in the risk of aSAH.[79] Smoking is an independent risk factor for sIA, and its effect is possibly synergistic with hypertension.[20] Furthermore, smoking seems to increase the risk of aneurysm rupture.[80] Alcohol use and its intensity may be associated with sIA rupture.[78,81] Type 1 and type 2 diabetes are not associated with an increased risk of aSAH.[49,78,82,83]

The three-layer structure of the arterial wall – tunica intima, tunica media and tunica adventitia – is present in the sIA wall, albeit increasingly disturbed as the aneurysm grows. The endothelial layer is disrupted, and an organised thrombus starts to form in the wall of the aneurysmal lumen. The wall lacks the internal elastic lamina – the disruption of which is among key features in the initial phase of the aneurysm formation – and the mural cells of the media and the adventitia become disorganised.[84]

The sIA wall is subject to continuous remodelling, and its extracellular matrix is renewed continuously.[67] In addition to mechanical stress, degradation caused by upregulated proteolytic enzymes contributes to the loss of the extracellular matrix.[84,85] The synthesis of the different components of the extracellular matrix is largely dependent on the smooth muscle cells of the medial layer of the aneurysm wall.[84] The medial layer is rearranged during the formation of the sIA: both hyperplasia of smooth muscle cells, known as myointimal hyperplasia, and degenerative changes due to apoptotic and necrotic cell death are variably observed in aneurysm walls. The risk of aneurysm rupture increases as loss of mural cells progresses and is greatest in aneurysms with thin, hypocellular walls and organised thrombi.[86] The shift from compensative hyperplasia and increased synthesis of the extracellular matrix components to predominantly degenerative changes and diminishing tensile strength is mediated by the loss of the smooth muscle cells of the aneurysm wall. The instigator of the protean inflammatory pathways and changes is not entirely clear.[87] Signs of the activation of both innate and acquired immune systems are observable in the sIA wall, and remodelling and the extent of the sIA wall degeneration are associated, *inter alia*, with endothelial activation, the magnitude of inflammatory cell infiltration, complement activation, several cytokine and growth-factor responses, oxidative stress and proteolytic enzymes secreted by the inflammatory cells.[87] However, a cascade of haemodynamic stress leading to endothelial dysfunction, endothelial dysfunction creating a proinflammatory milieu and a progressively dominating pro-degenerative inflammatory reaction in the

presence of oxidative stress can be hypothesised.[84,87] Recently, chronic periodontal inflammation has been linked to an increased risk of sIA formation and rupture.[88]

Of the different observed inflammatory markers, macrophages appear to be pathogenetically among the most central; infiltration of macrophages, particularly CD168-positive ones, is associated with degenerative changes and is found in ruptured sIAs more often than in non-ruptured ones.[86,87] Other specific examples of inflammatory changes include complement activation, the extent of which is associated with sIA degeneration and rupture.[89] Instead, while the accumulation of T-cells is more pronounced in degenerated aneurysms, CD3-positive T-cells appear to be dispensable for the formation and rupture of the aneurysm.[90]

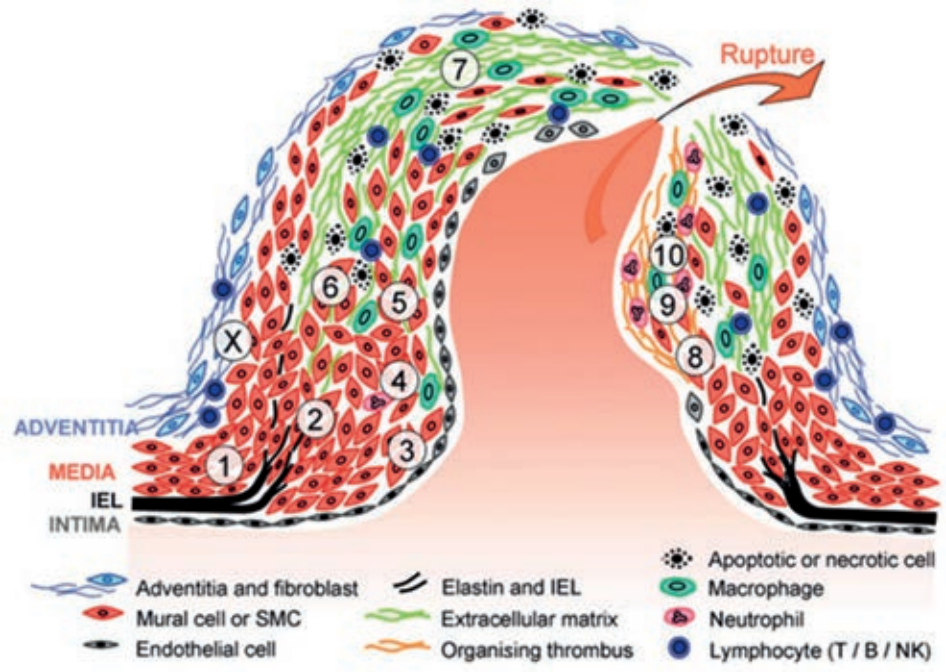

Figure 3 A hypothetical representation of the progression of the intracranial aneurysm wall degeneration. (1) Disrupted internal elastic lamina (IEL). (2) Myointimal hyperplasia. (3) Endothelial dysfunction and (4) chemotaxis are caused by haemodynamic stress. (5) Macrophages secrete growth factors stimulating matrix synthesis. (6) Necrotic and apoptotic death of smooth muscle cells (SMC) of the media. (7) Turnover of the extracellular matrix is slowed down because of the decellularisation increased activity of matrix metalloproteinases. The aneurysm ruptures when haemodynamic stress finally exceeds the tensile strength of the aneurysm wall. (X) Lymphocytes have a role in the immune response contributing to wall degeneration. Reprinted from Tulamo et al.[87]

2.1.4 Genomics of saccular intracranial aneurysm disease

Saccular IA disease is an example of a complex disease affected by both genetic and environmental factors and their interaction.[9,91,92] Under the liability model of polygenic inheritance, every individual can be assumed to have a latent continuous

liability to a given disease, composed of both genetic and non-genetic risk factors. The disease occurs when the total number of risk factors exceeds the so-called liability threshold.[93]

Saccular IAs are usually sporadic, with no known family history of sIAs or aneurysmal subarachnoid haemorrhage. However, a family history of aSAH or unruptured sIA (UsIA) is a significant risk factor for the formation of sIA: having a first-degree relative with sIA or aSAH confers a three- to fourfold risk of sIA.[20] The estimates of sIA prevalence in first-degree relatives of sIA and aSAH patients vary greatly. In a study of first-degree relatives of patients with sporadic aSAH in Hong Kong, their ages not reported, sIA prevalence was lower (2.4%) than the estimated computational general sIA prevalence of 3.2%.[20,94] In contrast, prevalence has been shown to rise with the increasing number of affected relatives; for example, in a prospective study with serial screenings of individuals with at least two first-degree relatives affected by aSAH or unruptured UsIA, the prevalence was 16%.[95,96] Having more than two affected first-degree relatives is associated with an additional risk.[97] Familial sIA disease, that is, disease in a patient having at least two first-degree relatives with either UsIA or aSAH, occurs in 10–15% of patients. Research suggests that the natural history of familial and sporadic sIA disease may be different: multiple sIAs are more frequent, the aneurysms tend to be located more often in the middle cerebral artery bifurcation, the aneurysms have a greater risk of rupture and the age at the haemorrhage is lower in familial sIA disease.[12,13,98-100] Data on the average size of the aneurysm at the rupture between familial and sporadic patients are conflicting. [98,99,101] The frequency of essential risk factors – female gender, smoking and hypertension – appears not to be different compared to the sporadic disease.[98,99,101]

Twin studies provide a robust way of estimating the heritability of a given trait or disease.[102] The only population-based twin study on aSAH found an increased concordance of aSAH in monozygotic twins, even though the absolute concordance rate was low in both monozygotic and dizygotic (3.1% versus 0.27%).[103] This study, based on the Nordic Twin Cohort, analysed only cases of ruptured aneurysms. As most saccular UIAs never rupture and go unnoticed, the heritability estimate of 0.41 derived from the study data is likely an underestimate of the heritability of the sIA disease itself.

Literature on the prevalence of unruptured sIAs in twin pairs is scarce. A review of the 14 published case reports, however, found that a clear location concordance (86%) of the aneurysms was noted among the monozygotic twins.[104] A similar finding was made when the twins identified in the large multicentre FIA study were analysed.[105] Intra-familial location concordance, albeit less pronounced, was also observed within the families of the FIA study.[106] The anatomic vulnerability of cerebrovascular architecture has been shown to affect sIA formation and possibly explains some cases of familial aggregation of the disease.[107]

Complex diseases present with several inheritance patterns, ranging from autosomal dominance to apparently sporadic cases. In particular, rare variants with

a relatively large effect are reportedly prone to cause familial disease, whereas accumulation of low-penetrance alleles and environmental factors could be more accountable for the apparently sporadic cases.[108,109] However, unless complete penetrance is assumed, the prevalence of the studied disease, as well as the family size of the proband families, has a profound effect on the observed rate of familial cases.[109,110] Patients without family history of the disease are common, both under a polygenic threshold liability model or when there is a large-effect rare variant with incomplete penetrance.[109,110] Spouses usually share environmental risk factors and other demographic characteristics to a greater degree than, e.g., siblings.[111] This presents a confounding factor in the analysis of complex diseases in families, even though the contribution of environmental factors to heredity of disease appears modest in most disesases.[112] In the context of the sIA disease, it is notable that the two most important modifiable, but also familial, risk factors to the sIA disease – hypertension and smoking – are more common in children with two affected parents.[17,113]

Propagation of the sIA disease in some sIA families suggests a defined pattern of inheritance. However, such a pattern is usually not evident from the family history or screening of first-degree relatives.[12,114,115] Numerous linkage studies have been performed in large families where carriership of a single genetic variant appears to be associated with a major risk of sIA disease. Numerous loci with a nominally significant association and a considerably smaller number of loci with a strong linkage-disequilibrium with the sIA disease have been identified in these studies, but only a few (11q25, 13q14.2, 19q13.3, Xp22.2) have been replicated.[115-123] No causative mutations have been identified based on the linkage studies. It is likely that there is true locus heterogeneity, and some mutations might be specific to a family or region.[91,115] The modest evidence for possible linkage across several chromosomes reflects the complex nature of the sIA disease; multiple genetic and environmental risk factors contribute to the total risk of the disease.[91]

Genome-wide association studies (GWAS) have found several risk loci for the sIA disease.[16,124-127] The risk variants with the strongest association to the sIA disease locate to the 9p21.3 locus that contains a gene cluster involved in the regulation of the cell cycle.[16,124,125,127] Other implicated genes participate in cell cycle regulation, cell adhesion, intracellular metabolism and inflammatory processes (Table 1).[16,124-127] The identified risk variants are estimated to explain less than 10% of the observed heritability of the sIA disease.[16,126] Notably, the GWASes on intracranial aneurysms have generally not separated the common saccular and the rare fusiform IAs, and they may have included some patients with fusiform IAs.

Table 1 Susceptibility loci for intracranial aneurysms identified in genome-wide association studies

Reference	Locus	Implicated genes	Population
Bilguvar et al. (2008), Kurki et al. (2014)[16,124]	2q33.1	*BOLL, PLCL1, ANKRD4*	Finland, Netherlands, Japan
Kurki et al. (2014)[16]	2q23.3	*LYPD6, MMADHC*	Finland
Yasuno et al. (2011), Low et al. (2012)[126,128]	4q31.23	*EDNRA*	Finland, other European, Japan
Kurki et al. (2014)[16]	5q31.3	*FSTL4*	Finland, Netherlands
Kurki et al. (2014)[16]	6q24.2	*EPM2A*	Finland, Netherlands
Foroud et al. (2014)[127]	7p21.1	*HDAC9*	USA (Caucasian), Netherlands
Kurki et al. (2014)[16]	7p22.1	*RADIL*	Finland
Bilguvar et al. (2008), Yasuno et al. (2010)[124,125]	8q11.12	*SOX17*	Finland, Netherlands, Japan
Bilguvar et al. (2008), Yasuno et al. (2010), Foroud et al. (2014), Kurki et al. (2014)[16,124,125,127]	9p21.3	*CDKNA2A, CDKN2B, CDKN2BAS*	Finland, other European, Japan, USA (Caucasian)
Yasuno et al. (2010)[125]	10q24.32	*CNNM2*	Finland, other European, Japan
Yasuno et al. (2010)[125]	13q13.1	*STARD13*	Finland, other European, Japan
Yasuno et al. (2010)[125]	18q11.2	*RBBP8*	Finland, other European, Japan

Rare and population-specific variants are not well assessed by genome-wide association studies, a limitation intrinsic to the methodology. Whole-exome or targeted exome sequencing has been employed in a relatively small but increasing number of studies investigating familial intracranial aneurysms,[129-136] implicating genes involved in the cell cycle *(PCNT)*,[134] regulation of angiogenesis *(ANGPTL6, ADAMTS5, RNF213)*,[131,135,136] collagen and elastin synthesis *(LOXL2)*[133] and endothelial function *(THSD1)*[132]. Mutations in *RNF213* and their relationship to intracranial aneurysms were investigated in a Western population and were

associated with moyamoya disease in Asian populations.[137] Biallelic deletion or inactivating mutation of *PCNT* cause microcephalic osteodysplastic primordial dwarfism type II, a rare genetic disorder associated with a high prevalence of intracranial aneurysms and other neurovascular abnormalities.[138]

2.1.5 Management of saccular intracranial aneurysms

Although large aneurysms may present with mass effect, cranial nerve compression, other sensory or motor deficit or seizures, the majority of UsIAs are asymptomatic and are found incidentally or in an sIA family screening.[139] In an attempt to overcome the lack of randomised, prospective data, computational simulation has been utilised: a model assuming an annual risk of 0.3–0.7% for *de novo* aneurysm formation and 1.0–2.0% for aneurysm rupture in individuals with two affected first-degree relatives and a small risk of treatment complications, serial screening was found to be cost-effective.[140] Screenings of individuals with at least two first-degree relatives affected by aSAH are recommended by both the European Stroke Organisation and American Heart Association guidelines.[141,142] In a serial screening study of 458 individuals with at least two first-degree relatives with aSAH or UsIA, 51 (11%) individuals with UsIA were identified in the first screening, the total number increasing to 72 (16%) in serial screenings.[96]

The risk of rupture of a given aneurysm is highly variable and dependent on several patient- and aneurysm-specific factors.[143] Available predictive data on the risk of rupture is mainly based on the large prospective ISUIA and UCAS cohorts.[77,144] These and the PHASES score,[143] derived from the results of the ISUIA and UCAS studies and four smaller prospective cohorts, do not incorporate known risk factors such as smoking, family history of subarachnoid haemorrhage and several aneurysm-related haemodynamic factors.[77,144-147] Aneurysm growth is a risk factor aneurysm rupture, and most of the known risk factors for aneurysm rupture predispose to aneurysm growth as well.[148,149]

The optimal management of unruptured intracranial aneurysms remains uncertain. Only one randomised trial on UsIA treatment, notably limited to cases where the optimal treatment modality of the aneurysm was deemed unclear, has been published.[150] Operative management, whether surgical or endovascular, aims to permanently occlude the aneurysm. Endovascular treatment and neurosurgical clipping have been directly compared on a large scale only in the context of the aSAH.[151] The large ISAT trial compared endovascular and surgical treatments in cases where the optimal treatment was deemed equivocal. The majority of enrolled patients presented with good clinical grades and with aneurysms in the anterior circulation. The trial found lower combined rates of death and disability (relative risk reduction of 24%) at the one-year follow-up in the patients treated by endovascular coiling.[151] Other considerably smaller studies have reported similar results.[152] Evidence for the comparative safety of endovascular treatment other than simple coiling is lacking.

The results based on studies of patients with aSAH cannot be directly extrapolated to the treatment of UIAs, however. The treatment of ruptured IAs is associated with greater morbidity and mortality than the treatment of unruptured IAs.[151,153,154] Nevertheless, neither neurosurgical nor endovascular treatment of UIAs is free of risk of complications.[153,154] In the most recent meta-analyses, the treatment-related risk of UIA closure has been approximately 5% for endovascular treatment and 7–8% for surgical treatment.[153-155] The randomised trial by Darsaut et al. found no statistically significant difference in the rate of treatment failure – the primary outcome of the trial – nor in the postoperative morbidity between the treatment modalities.[150]

Conservatively managed UIAs are often subject to follow-up imaging. The optimal frequency of follow-up imaging is unclear, and aneurysm growth is not always linear.[156,157]

No pharmacologic therapy has been approved for the reduction of the risk of rupture. Observational data and murine aneurysm models have suggested that aspirin (ASA) prevents aneurysm formation and rupture.[158-160] A more selective inhibition of prostaglandin signalling has yielded promising results in a murine animal model as well.[161] No randomised clinical trials on the effect of anti-inflammatory drugs on prevention of sIA formation or growth have been published. The protective effect of hypercholesterolaemia observed in retrospective studies has been hypothesised to relate to statin use.[77,92] Statins, in addition to and independent of their lipid-lowering effect, have been shown to favourably modulate the inflammatory pathways activated in animal models of abdominal aortic aneurysms, but their effects on the risk of both aortic and intracranial aneurysm progression and rupture have been shown to conflict in retrospective epidemiological studies.[162-164]

2.2 FUSIFORM INTRACRANIAL ANEURYSMS

Intracranial fusiform aneurysms (Figures 1 and 4) comprise a rare and poorly defined group of arterial pathology. The trunks (segments) of the intracranial extracerebral arteries may dilate, elongate and become tortuous. Dilatations of the trunks of cerebral arteries have been called both fusiform and dolichoectatic aneurysm and intracranial dolichoectasia (IADE).[8,165] As a descriptive term, dolichoectasia refers to arterial elongation and distension not necessarily manifesting as focal dilatation. There are no established diagnostic criteria for differentiation between these entities; the Smoker criteria based on elongation and dilatation of the basilar artery are used to diagnose vertebrobasilar IADE in research settings.[166,167] The clinical presentation of 'the fIA disease' is varying.[8,165] In a meta-analysis of 827 fIA patients, 40% presented with brain infarction, 28% with mass effect, 30% as an incidental finding, and only 2% with subarachnoid haemorrhage.[165]

The largest published patient series and analyses of fIAs have focused on the most common site of the disease, the vertebrobasilar arteries.[165,168] However, fIAs can be present in any large cerebral artery trunk and may extend to involve arterial bifurcation.[169-173] Frequency estimates of IADE, with differing definitions, range from 3% to 17% in patients with ischaemic stroke.[174,175] In the elderly, stroke-free population, IADE was observed in 19–52% depending on the definition of dolichoectasia, with an 11% prevalence of vertebrobasilar dolichoectasia as defined by the Smoker criteria.[167]

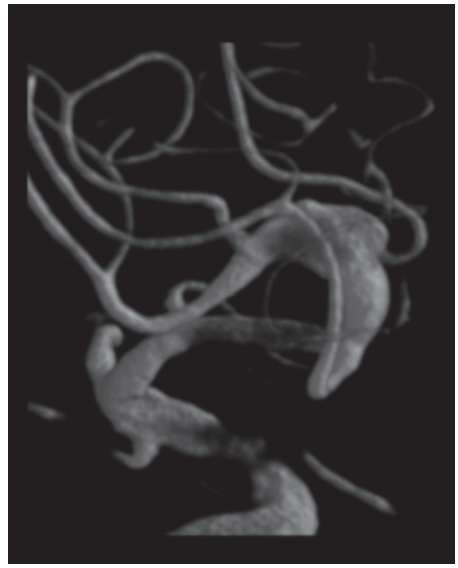

Figure 4 Fusiform intracranial aneurysm involving the M1 segment of the middle cerebral artery

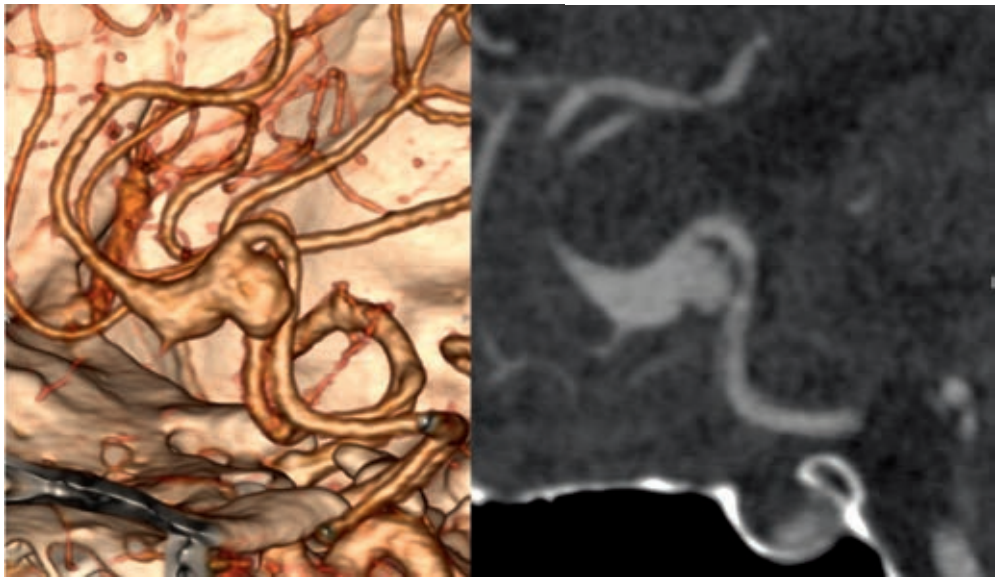

Figure 5 Fusiform intracranial aneurysm involving the anterior cerebral artery.

2.2.1 Aetiology and pathophysiology of fusiform intracranial aneurysms

A distinct majority of fusiform intracranial aneurysms are located on the basilar artery, often extending to other arterial trunks of the vertebrobasilar complex.[176] It has been suggested that the obtuse angle of the basilar bifurcation would create a situation analogous to the abdominal aorta, where the aortic bifurcation is suggested to create reflection waves contributing to the regional susceptibility of the infrarenal aorta to aneurysm formation.[8,177,178]

In a few cases, fusiform arterial dilatation is associated with a specific metabolic disease affecting the smooth muscle cells of the media.[8,176] Fabry's disease, an X-linked lysosomal storage disease, and Pompe disease, another lysosomal storage disease, often lead to intracranial dolichoectatic arterial dilatations due to the weakening of the arterial wall.[179,180] In addition, there are case reports of vertebrobasilar fIA occurring in conjunction with neurofibromatosis type 1 (NF1), Marfan syndrome and other monogenic syndromes primarily affecting the extracellular matrix.[34,181-184] Recently, somatic mutations in the platelet-derived growth factor receptor β (*PDGFRB*) have been implicated as a potential pathogenetic factor behind fIA formation.[185]

The histopathology of fIA disease has not been adequately studied. In a series of eight fIAs[186] and 13 acute intracranial arterial dissections at different points of time,[187] fragmentation of the internal elastic lamina, neoangiogenesis within the thickened intimal layer, thrombus formation, and repetitive intramural haemorrhage were observed.[186,187] It is notable that similar changes are described in the surgical specimens of both aortic aneurysms[188,189] and saccular intracranial aneurysms.[190] As in many of the 13 patients, the acute dissection transformed into an fIA; the authors suggest the two disease entities might share similar underlying mechanisms.[187] Day et al. draw a similar conclusion from their own series of 40 patients with fusiform MCA aneurysms and the cases published in the literature.[191]

2.2.2 Management of fusiform intracranial aneurysms

The management of fusiform and dolichoectatic aneurysms is challenging, sometimes impossible. An optimal treatment strategy would effectively prevent the thromboembolic and ischaemic and haemorrhagic complications and prevent or remedy brain compression symptoms. Diverse surgical procedures – clip reconstruction, clip-wrapping, proximal trapping with bypass, aneurysm excision with end-to-end anastomosis – have been employed in the treatment of ruptured and unruptured fIAs with varying success.[192] Endovascular procedures used in the treatment include vessel sacrifice, stent-assisted coiling, and flow diversion.[8,193]

Ischaemic presentation and complications are common. The role of antiaggregatory or anticoagulant medication in fusiform IAs is unclear.

Anticoagulants do not seem to provide an advantage but may confer an increased risk of haemorrhage.[194,195] Strict blood pressure control is recommendable.[8]

In basilar fusiform aneurysms, a diameter of over 10 mm or aneurysmal enlargement have been proposed as indications for operative management.[8,193,196] The considerable technical difficulties associated with both endovascular and microsurgical treatment, as well as the burden of different comorbidities of the often elderly fIA patients mandate individualised treatment.[192,197]

2.3 NEUROFIBROMATOSIS TYPE 1

Several hereditary disorders such as Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, fibromuscular dysplasia, neurofibromatosis type 1 (NF1) and sickle cell disease are suspected to be associated with an increased incidence of intracranial aneurysms.[29,198,199] Notably, autosomal dominant polycystic kidney disease (ADPKD), a monogenic condition with the most consistently verified connection to sIA disease, also has extrarenal complications.[200] Estimates of IA prevalence among ADPKD patients range from 9% to 14%.[11]

NF1 is a relatively common monogenic neurocutaneous syndrome inherited in an autosomal dominant manner and occurring at an estimated frequency of 1:2000.[201] A substantial 50% of the cases are caused by *de novo* mutations. NF1 does not exhibit reduced penetrance, but its clinical manifestations and severity vary between and within NF1 families. *NF1*, located on 17q11.2, codes the tumour suppressor protein neurofibromin, which is involved in the regulation of the mitogenic Ras signalling pathway. Homozygous inactivation of *NF1* is incompatible with life, and the clinical manifestations of NF1 relate to a somatic "second-hit" inactivation.[202] The classical manifestations of NF1, required for the diagnosis, include cutaneous café-au-lait macules and cutaneous or plexiform neurofibromas, axillary and inguinal freckling, the so-called Lisch nodules of the iris, osseous dysplasia and, in childhood, optic pathway gliomas.[22] NF1 is associated with a significantly increased risk for various cancers: the lifetime risk is approximately 60%.[203]

Tumours of the central and peripheral nervous systems are characteristic of NF1: the syndrome is associated with a 15–20% lifetime risk of low-grade gliomas and an 8–13% lifetime risk of malignant peripheral nerve sheath tumours.[204] However, the risk of a number of other malignancies is increased as well.[203] Impairment of neuropsychological performance and ADHD are common among children with NF1.[205]

A number of vascular complications have been attributed to NF1. Luminal narrowing due to intimal hyperplasia, the most important clinical consequence of which is renal artery stenosis, has been linked to NF1.[206,207] In the cerebral circulation, vascular dysplasia may lead to moyamoya disease.[25] Poststenotic aneurysms sometimes occur in the peripheral arteries of NF1 patients. Based on case reports and a small patient series of NF1 patients, the association of intracranial aneurysms and NF1 has been reported as well.[26,27,29,208-215] Additionally, two retrospective series of 47

and 22 NF1 patients who had undergone cerebral angiography reported an increased prevalence of IAs (11% and 9%).[26,29] The exact mechanism with which the mutations of *NF1* would lead to specific organ complications, including vascular anomalies, are mostly unknown.[23,202] Heterozygous inactivation of *NF1* leads to increased endothelial proliferation *in vitro* and heterozygous inactivation of *NF1* in the myeloid cell line accentuated formation of arterial aneurysms in a murine aneurysm model.[216,217]

The principal goal of NF1 management is early detection and management of its serious complications. Despite the relatively well-characterised molecular pathogenesis of the benign and malign tumours associated with NF1, no specific drug treatment has yet been discovered.[23] Optic pathway gliomas associated with NF1 have a relatively indolent natural history.[218] An inhibitor of MEK (mitogen-activated protein kinase kinase), a protein kinase involved in the MAPK/ERK pathway, selumetinib, has shown some promise in the treatment of plexiform neurofibromas.[219] Malignant peripheral nerve sheath tumours are associated with an aggressive course and a poor prognosis; curative therapy requires radical surgery.[23]

2.4 ABDOMINAL AND THORACIC AORTIC ANEURYSMS

2.4.1 Abdominal aortic aneurysms

Abdominal aortic aneurysm (AAA), defined as a dilatation of the infrarenal aorta to a diameter over three centimetres, is a relatively common disorder.[32] AAA rupture is associated with very high mortality and is an important cause of death in the elderly population.[220,221]

2.4.2 Epidemiology of abdominal aortic aneurysms

The prevalence of AAA varies considerably by age. A meta-analysis of 26 studies estimated the prevalence of 7.9 per 100 000 in the age group 40–44 years and 2,274 per 100 000 in the age group 75–79 years.[222]–Screening programs of elderly men in Sweden[223], the United Kingdom[224] and the United States[225], shown to be cost-effective, have increased the number of diagnosed unruptured AAAs. The role of screening in the reduction of mortality due to AAA rupture has been questioned, however.[226] The screening of women has not been implemented due to lower prevalence; therefore, these screenings have not been investigated in a sufficiently powered randomised setting. The available evidence and computational modelling do not endorse population screenings of women.[33,227,228]

AAA rupture is associated with a considerable risk of sudden death; approximately 50% of patients die before reaching a hospital.[220,229] The estimated incidence of AAA rupture in Finland, based on retrospective register data and subject to some degree of misclassification, is 16.4 per 100 000 person-years in the population over 50 years.[220] The incidence of AAA rupture has been declining in the developed world.[220,230-232]

2.4.3 Aetiology and pathophysiology of abdominal aortic aneurysms

Most AAAs are fusiform or concentric dilatations of the aorta. Saccular AAAs are rare, comprising <5% of all AAAs.[233] In contrast to saccular intracranial aneurysms, saccular aneurysms of the aorta often originate from a specific and definable cause; traumatic or infectious aetiology is typical.[233]

Family history of AAA is consistently reproduced and is a clinically significant risk factor for AAA.[234-236] The estimated heredity of AAAs, based on twin studies, is substantial: 70%–80%.[237,238] Specific monogenetic syndromes, however, are less common causes of AAA than TAA. Many of the genetic syndromes associated with TAA, including the vascular subtype of Ehlers-Danlos syndrome, Marfan syndrome and Loeys-Dietz syndrome,[239-241] can lead to changes in the abdominal aorta. The pathology of AAAs, however, is most often multifactorial, and environmental factors have a considerable effect on and probably interact with genetic factors predisposing to AAA formation.[242] The association of smoking and AAA is noteworthy, and it has been estimated to account for up to 80% of large (>4 cm) AAAs.[243] Other risk factors for AAA, shared with atherothrombotic occlusive arterial disease, include male sex, increasing age, hypertension, and hypercholesterolaemia.[244] Interestingly, despite the strong relationship of diabetes and arterial disease, diabetes is associated with both a decreased aneurysm prevalence and slower aneurysm growth.[245]

AAAs and occlusive atherosclerotic disease share several risk factors, including hypertension, smoking, hyperlipidaemia, male sex and increasing age, and the wall of the affected aorta usually exhibits clear atherosclerotic changes.[246,247] However, the gene expression patterns of AAAs and aortic walls affected by occlusive atherosclerotic disease differ significantly.[247] Some of the genetic risk variants predisposing to AAA are not associated with atherosclerosis – and vice versa – further suggesting that the genetic pathways underlying the considerable heredity of AAA are at least partly unique to AAA.[248,249] Genome-wide association studies have found an association to a limited number of loci localising to genes involved in inflammatory pathways, genetic regulation and cellular metabolism.[250] Recently, a whole-genome sequencing study employing a novel machine-learning algorithm has implicated several converging genetic pathways including genes involved in angiogenesis, cell-to-cell communication, cellular metabolism and, in particular, immune response.[251]

The haemodynamic factors of the infrarenal aorta are assumed to predispose the artery to dilatation in the presence of wall degeneration: the haemodynamics of the infrarenal aorta are characterised by disturbed blood flow, low and oscillatory wall shear stress and retrograde pressure waves associated with the iliac bifurcation.[252] The usually present intraluminal thrombus is biologically active and contributes to the continuing damage to the aneurysmal wall.[253]

Histopathologic changes in human specimens of AAA include proteolytic fragmentation of the extracellular matrix, cell death in the media and immune cell infiltration. Neovascularisation and mural haemorrhages are common.[188]

Importantly, similar changes are observed in fusiform intracranial aneurysm specimens.[186,187]

2.4.4 Management of abdominal aortic aneurysms

Ruptured AAA is a surgical emergency associated with considerable immediate and postoperative mortality – up to 90% – necessitating prompt treatment with either open surgical or endovascular aortic repair.[220,254] Most treated AAAs, however, are unruptured.[220] A maximum diameter of 5.4 cm is considered an indication for aneurysm repair in patients fit for an elective procedure.[32] Endovascular aortic repair (EVAR) is being used more often in both elective and acute settings;[220] EVAR requires suitable anatomy and is not suitable for all AAAs but has the advantage of being less invasive.[255]

Pharmacologic inhibition of AAA growth – of significant interest in fusiform IAs and dolichoectasia – has been investigated in several *in vitro* studies, animal models and clinical trials.[256,257] Notable agents halting AAA progression in experimental models include those targeting the immune and inflammatory pathways and the ECM degradation.[257] Clinical trials have been conducted on propranolol, a β-blocker; several antibiotics (roxithromycin, azithromycin, doxycycline); pemirolast, a mast cell inhibitor; and perindopril, an angiotensin-converting enzyme inhibitor.[257] Propranolol inhibited AAA growth in murine models and was among the first drugs to be investigated in a randomised clinical trial, but failed to show an effect on human AAA growth. Antibiotics have been investigated because of their suspected role in *Chlamydia pneumoniae* in AAA development.[258] The results of trials with roxithromycin and azithromycin have been conflicting, and their effect on limiting AAA expansion is moderate at most. Doxycycline, in addition to its antibiotic effect, acts as an MMP inhibitor. A three-month course of doxycycline did not significantly slow AAA progression in a clinical trial, and continuous therapy was associated with a faster rate of progression than placebo.[259] The trials on pemirolast and perindopril have yielded negative results.[260,261] Observational data on the effect of statin use on AAA progression are conflicting. As statins are frequently prescribed to patients with AAA for other indications, a randomised trial might not be doable.[257,262]

2.4.5 Thoracic aortic aneurysms

Thoracic aortic aneurysms (TAA), defined as a dilatation of at least 50% greater than the expected diameter of the aorta, are usually clinically silent. However, complications associated with TAA, rupture and aortic dissection, are associated with significant mortality.[31]

2.4.6 Epidemiology of thoracic aortic aneurysms

Research on the epidemiology of thoracic aortic aneurysms is impeded by the same limitations that affect the epidemiological studies on intracranial and abdominal aortic aneurysms. Furthermore, the normal diameter of the thoracic aorta varies with location, age and gender, affecting the cut-off value for diagnosis of TAA, defined as at least a 50% increase in the expected normal diameter.[31,263] The incidence varies from 6 to 10.4 per 100 000.[31] The prevalence ranges from 0.16% to 0.34%.[264,265]

2.4.7 Aetiology and pathophysiology of thoracic aortic aneurysms

Thoracic aortic aneurysm and dissection are pathologically and aetiologically connected diseases: connective tissue disorders such as Marfan syndrome and vascular Ehlers-Danlos syndrome predispose to both TAA and aortic dissection, and medial degeneration is encountered in both patient groups even without specific predisposing genetic syndromes.[266,267]

Despite the relatively pronounced role of hereditary factors in TAA, the majority of TAAs occur in aged patients with traditional cardiovascular risk factors (smoking, hypertension, male sex). The role of atherosclerosis is unclear, however. Specifically, macroscopic atherosclerotic changes are common in aneurysms occurring below the ligamentum arteriosum but are rare above it.[268] As in AAA, diabetes is negatively associated with TAA.[269] Bicuspid aortic valve (BAV) is associated with TAA in 40–50% of cases.[270,271] BAV is often familial, but detailed knowledge of its molecular genetics is lacking.[270] The genetic syndromes associated with TAA include Marfan syndrome, vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Shprintzen-Goldberg syndrome and aneurysms-osteoarthritis syndrome.[271]

Up to 20% of the patients with TAA do not present with a predisposing syndrome, but have a first-degree relative with TAA; these patients tend to be younger than sporadic TAA patients.[271] In several cases, TAA appears to segregate in an autosomal dominant fashion with variable expression.[271] Linkage studies have implicated numerous associated loci, and underlying genetic heterogeneity appears to be significant. Many identified causative mutations are linked to the same pathways as the syndromic forms of TAA, e.g., the *TGF-β* pathway, the extracellular matrix and the cytoskeleton.[271] The identified genetic risk factors for TAA are mostly not shared with AAA.[242]

Saccular TAAs, like those of the abdominal aorta, are usually linked to bacterial infection or penetrating arterial ulcers.[233]

2.4.8 Management of thoracic aortic aneurysms

Treatment of thoracic aortic aneurysms mirrors that of abdominal aortic aneurysms: rupture is a devastating event associated with high case fatality and requires immediate operative treatment, whereas aneurysms found incidentally or through

family screening are followed up or treated depending on their size and other factors. Operative treatment is indicated when the diameter of the aneurysm exceeds a threshold dependent on patient- and aneurysm-related factors, whereas smaller aneurysms are followed up. A diameter over 5.5 cm indicates operative management of an aneurysm. The threshold is lower for aneurysms associated with bicuspid aortic valve or syndromic TAAs.[31]

There is limited evidence for the efficacy of β-blockers and angiotensin receptor blockers (ARBs) in limiting aortic expansion in patients with Marfan syndrome. β-blockers decrease the force of the myocardial contraction, thus reducing the stress to which the aortic wall is subjected.[267] ARBs have been suggested to be beneficial in Marfan syndrome because of their antagonistic activity on the transforming growth factor (TGF) pathway, the regulation of which is deranged in Marfan syndrome.[272] There are no clinical trials comparing ACE inhibitors and ARBs, and comparison to β-blockers has demonstrated only noninferiority.[272]

2.5 AORTIC PATHOLOGIES AND INTRACRANIAL ANEURYSMS

The association of bicuspid aortic valve (BAV) and intracranial aneurysms has been investigated in three studies. A retrospective analysis of 678 patients with BAV and a systematic screening of 61 BAV patients for IA found an IA prevalence of approximately 10% (7.7–9.8%).[3,273] In a reverse approach in a retrospective analysis of the imaging studies available for 317 IA patients, the co-occurrence of IA and BAV was modest, 0.6%. In comparison, the population prevalence of BAV is approximately 1%.[274] BAV is associated with other aortic abnormalities, including TAA, thoracic aortic dissection and coarctation of the aorta, most likely because of an underlying intrinsic defect in the aortic media.[270] The observed propensity for IA is hypothesised to relate to this arteriopathy.[3] The screening of patients with BAV for IA has been recommended.[275]

The co-occurrence of coarctation of the aorta and intracranial aneurysms has been investigated in three systematic screening studies of patients with coarctation of aorta (CoA).[4,276,277] These studies, with a combined cohort of 260 patients, reported a rather uniform IA prevalence, approximately 10% (10.3–11.6%). The mean ages of the patient cohorts, 42 years,[276] 34 years[277] and 29 years,[4] are notable. Increasing age was an independent risk factor for IA in all the studies, and considerably high estimates for the cumulative IA prevalence in CoA patients have been derived.[277] Aortic coarctation is associated with secondary hypertension, a risk factor for intracranial aneurysms.[48] No association of hypertension or the poor control thereof with the occurrence of IA was found in the three cohorts.[4,276,277] Screening for intracranial aneurysms in patients with coarctation of the aorta has been recommended.[275]

Aortic dissection and aortic aneurysms in patients with intracranial aneurysms, or vice versa, have been investigated in a few retrospective studies. Some studies group all aortic aneurysms together and some include only AAA or TAA. Aortic dissection, a condition often related to TAA, has been studied both separately and

together with TAA. The prevalence of IA among aortic aneurysm patients ranged from 9.0% to 20.3%.[36,38,39,41] Higher prevalence rates, 19.7%–32.0%, have been reported in association with aortic dissection.[41,278] Interestingly, in one cohort, anterior circulation IAs occurred more often with aneurysms of the ascending thoracic aorta, whereas aneurysms of the internal carotid artery occurred more often with abdominal aortic aneurysms.[38] Two patient cohorts with undefined IA have reported an AAA prevalence of 7.2% and a TAA prevalence of 4.7%.[35,37] A large cohort of vertebrobasilar fusiform and dolichoectatic aneurysms included a significant proportion (13%–18%) of patients with AAA.[34,40] Furthermore, the diameter of the thoracic aorta of IA patients and patients with dolichoectatic dilatation of the internal carotid artery is increased in comparison to controls.[279,280]

A meta-analysis of GWAS cohorts of IA, AAA and TAA patients found neither evidence for a shared polygenic effect among the different diseases nor shared risk loci between any two of the three diseases with a genome-wide significance.[281] Interestingly, a variant localising to the same 9p21.3 locus that has been consistently associated with IAs has a protective effect against AAAs.[250]

3 AIMS OF THE STUDY

The aim of the study, presented in the following three articles, were as follows:

I) To re-evaluate the often-proposed association of NF1 and intracranial aneurysms in population-based IA and NF1 registries.

II) To identify sIA families in which both parents were carriers of sIA disease and study its propagation to their children, and to study the effect of familial versus sporadic sIA disease on the sIA risk of the offspring.

III) To study the association of aortic aneurysms and intracranial aneurysms in a population-based registry of sIA and fIA patients, and, additionally, to evaluate a putative genetic connection between fusiform IA and AA.

4 NEUROFIBROMATOSIS TYPE 1 IS NOT ASSOCIATED WITH SUBARACHNOID HAEMORRHAGE

4.1 INTRODUCTION

Neurofibromatosis type 1 (NF1) is a relatively common autosomal dominant genetic disorder caused by a mutation in the *NF1* gene on the long arm of chromosome 17.[21] The clinical hallmarks of NF1 include café-au-lait spots, neurofibromas, and Lisch nodules of the iris, yet NF1 can affect several organ systems (Tables 2 and 3).[22,23] Even though NF1 displays 100% penetrance, the clinical severity is highly variable even within one NF1 family.[202] Cardiovascular complications that have been associated with NF1 include stenosis of pulmonary, renal, mesenteric and intracranial arteries, moyamoya disease–and intracranial aneurysms (IAs).[23-27] The association between IAs and NF1, however, has been contentious during the last two decades.[26,28-30]

IAs are estimated to be carried by approximately 3% of the general population.[20] Known risk factors for IAs include age, female sex, smoking, hypertension, family history for IAs and autosomal dominant polycystic kidney disease (ADPKD).[20,78] The genetic mechanisms predisposing to the complex IA disease are, so far, unclear.[16]

We cross-linked two large Finnish population-based patient cohorts with the hospital diagnoses from the nationwide registry. Our aim was to find out if there is any additional evidence to support the consumption that NF1 is associated with intracranial aneurysms by determining the prevalence of NF1 in a population-based cohort of IA patients and, on the other hand, the prevalence of SAH and IAs in a national register of NF1 patients.

Table 2 Diagnostic criteria for NF1: two or more of the following

Criterion
Six or more café-au-lait macules with diameters >5 mm in prepubertal and >15 mm in postpubertal patients
Two or more neurofibromas of any type or one plexiform neurofibroma

Axillary or inguinal freckling
Optic glioma
Two or more Lisch nodules of the iris
A distinctive osseous dysplasia (sphenoid wing dysplasia, bowing of the long bones or pseudoarthrosis)
A first-degree relative diagnosed with NF1

Table 3 Manifestations of NF1 in different organ systems

Pigmentary abnormalities	Café-au-lait macules, axillary freckling, Lisch nodules
Neurofibromas	Benign Schwann-cell tumors containing several cell types
Plexiform neurofibromas	Benign tumors arising from multiple nerve fascicles and growing along nerves. Usually congenital but have potential to grow and become malign
Skeletal deformities	Osteoporosis/osteopenia, dystrophic scoliosis, sphenoid wing dysplasia, tibial dysplasia and pseudarthrosis, short stature, increased head circumference
Cardiovascular abnormalities	Idiopathic and secondary hypertension, vascular dysplasia
Neurocognitive deficits	Visuospatial and visuomotor deficits, learning disabilities, ADHD
Tumours of nervous system	Glioma of the optic pathway, malignant peripheral nerve sheath tumors, brainstem glioma, glioblastoma
Other tumours	Gastrointestinal stromal tumors, breast cancer, leukaemia and lymphoma, especially myeloid leukaemia, phaeochromocytoma, duodenal carcinoids, rhabdomyosarcomas.
Endocrine abnormalities	Precocious or delayed puberty
Other manifestations	Focal T2 hyperintensities of the brain (UBOs)

4.2 METHODS

The Kuopio IA Database (www.kuopioneurosurgery.fi) includes all ruptured and unruptured IA cases admitted to the Kuopio University Hospital (KUH) from its defined Eastern Finnish catchment population since 1980.[43] The prevalence of NF1 in the 4,543 patients with unruptured IA or aSAH, as well as their 19,644 first-degree relatives, was analysed. In a reverse approach, the 1,410 NF1 patients of the Finnish NF1 Registry were analysed for unruptured IA and aSAH diagnoses between 1987 and 2014.[201]

4.2.1 KUH catchment population

Neurosurgery of Kuopio University Hospital (KUH) has been the sole provider of full-time acute and elective neurosurgical services in its catchment area in Eastern Finland since 1977. The catchment area consists of four central hospitals, each with their own neurological units and catchment areas. During the recruitment period of the present study, from 1980 to the end of 2015, the geographic KUH area has not changed. The population has decreased from 882,671 to 815,021.[282] The median age has risen from 37 to 42 years in men and from 40 to 45 years in women, while the proportion of men has remained at 49%.[13,282]

4.2.2 Kuopio Intracranial Aneurysm Patient and Family Database

All patients admitted to KUH with unruptured or ruptured IAs have been recorded in the Kuopio IA Database (www.kuopioneurosurgery.fi) since 1980, prospectively since 1990. The clinical data from the hospital periods and follow-up visits have been recorded. The family history for IA has also been recorded: an IA family contains at least 2 affected first-degree relatives.[13]

4.2.3 Identification of NF1 in 4543 IA patients in the Kuopio IA Database

Clinical data including prescribed drugs and causes of death have been imported from the national registries.[43,47] The first-degree relatives of the 4543 IA patients were retrieved from Population Register Centre of Finland, using the personal identity codes, and their clinical data were also retrieved from the nationwide registries. The Kuopio IA Patient and Family Database was cross-linked with the Finnish electronic hospital diagnosis registry (Care Register for Health Care HILMO, managed by the Finnish Institution for Health and Welfare) that covers all secondary and tertiary centres in Finland and includes all medical specialties. Patients with NF1-related diagnoses were searched with the ICD-8, ICD-9, and ICD-10 codes (when applicable) for NF1, as well as unspecified neurofibromatosis (743.4, 237.70 and 237.71, and Q85.0 and Q85.00, respectively), café-au-lait spots (709.09 and L81.3), benign neoplasms of brain, cranial nerves and peripheral nerves (225, 225, and D33 and 225, 229, and D36), nerve root and plexus disorders (357, 353 and G54), mononeuritis of the upper and the lower limb (357, 354 and G55, and 355 and G56), disorders of

continuity of bone (733.8 and M84), and malignant neoplasms of peripheral nerves (192.4, 192, and C47). The records of the patients potentially carrying NF1 were carefully re-reviewed to confirm or exclude the diagnosis of NF1.

The hospital diagnoses of the 19644 first-degree relatives of the 4543 patients were searched for NF1 (743.4, 237.70 and Q85.0). Finally, the patient records of the IA patients with first-degree relative(s) with NF1 were screened for signs of NF1.

4.2.4 Identification of IA among 1410 NF1 patients in the Finnish NF1 Registry

The Finnish NF1 Registry is a nationwide registry of all the Finnish NF1 patients who had visited any of the five university hospitals or 15 central hospitals of Finland between 1987 and 2011, with NF1 in their medical records.[201] The NF1 diagnoses have been ascertained by the re-review of the medical records, and all cases fulfil the NIH diagnostic criteria for NF1 (Table 2). The present NF1 cohort comprises of 1,410 patients, 48% males. A ten-fold control cohort (n = 14,030), individually matched by the age, sex and place of residence at the time of NF1 cohort entry, was retrieved from the Population Register Centre of Finland. The 1,410 NF1 patients had been followed up from the first hospital visit associated with NF1 between 1987 and 2011, and the 14,030 controls had been followed up from the NF1 cohort entry date of their respective NF1 patients. The follow-up time ended at death, emigration, December 31, 2014, or the date of occurrence of an IA diagnosis (unruptured IA or aSAH). The 1410 NF1 patients and their 14,030 controls were linked with the same Finnish electronic hospital diagnosis registry (Care Register for Health Care) that was used to identify NF1 diagnoses in the IA Patient and Family Database, and patients with diagnoses of subarachnoid haemorrhage (SAH) (ICD-9 431, ICD-10 I60.1-I60.9) and unruptured IAs (ICD-9 437.3, ICD-10 I67.1) were identified. Their diagnoses were verified from medical records. In addition, the death records of the 249 NF1 patients deceased before July 1, 2013, were reviewed to identify the diagnoses of aSAH and unruptured IAs.

4.2.5 Statistical methods

Incidence of diagnoses in the NF1 cohort was analysed using the Cox proportional hazards model with stratification by a factor that indexed matched sets of NF1 patients and controls.

4.2.6 Ethical aspects

The Kuopio IA Patient and Family Database has been approved by the Ethical Committee of the KUH, the Finnish Ministry of Social Affairs and Health, and the National Institute for Health and Welfare and written informed consent was obtained from all patients. The NF1 database was approved by the Ethics Committee of the Southwest Finland Hospital District, the Finnish Ministry of Social Affairs and

Health, and the National Institute for Health and Welfare waiving the need for patient consent, since patients were not contacted during data collection.

4.3 RESULTS

4.3.1 Prevalence of NF1 in the Kuopio IA cohort

Among the 4543 IA patients, a total of 156 patients with diagnoses potentially related to NF1 were identified. Only two of the 156 IA patients had a recorded diagnosis of NF1, but the other proved to have tuberous sclerosis (Q85.1), mislabelled as NF1. Of the 156 IA patients, another five had symptoms suggestive of NF1: however, one had clinical features and histological findings indicative of schwannomatosis; two had a confirmed diagnosis of neurofibromatosis type 2 (NF2); one had features indicative of NF2; and one had a suspected neurofibroma that turned out to be a leiomyoma. Five first degree relatives to the 4543 IA patients had the diagnosis of NF1, but none of their three IA carrying relatives had clinical signs of NF1. The prevalence of NF1 was one per 4,543 (22/100,000) in the IA cohort. The single IA patient with NF1 was a 46-year-old woman with incidental bilateral middle cerebral artery bifurcation IAs while her cerebral vasculature was otherwise normal in angiography.

4.3.2 Diagnoses of unruptured IAs or SAH in the NF1 cohort

The 1,410 NF1 patients and their 14030 matched controls had been followed up for totals of 21,220 and 229,307 person-years with mean follow-up times of 15.0 and 16.3 years, respectively. Only one unruptured IA was found in autopsy in the NF1 cohort and no cases of unruptured IA were reported during the follow-up, whereas 19 unruptured IA cases had been found among the controls during follow-up. During follow-up, five of the 1,410 NF1 patients and 34 of the 14,030 controls had been diagnosed with SAH, a hazard ratio of 1.8 (95% CI 0.69 to 4.67, $P = 0.234$), but in a closer review of patient records and death certificates, only one NF1 patient had had SAH of aneurysmal origin. In addition, one patient with aneurysmal SAH was found by reviewing the death certificates of the NF1 cohort.

4.4 DISCUSSION

4.4.1 Key results

To our knowledge, this is the first comprehensive study on the occurrence of NF1 in a large population-based IA cohort (n = 4,543), and unruptured IA or aSAH in a population-based NF1 cohort (n = 1410). Only one patient with confirmed NF1 was found among the 4,543 IA patients admitted between 1980 and 2015 to KUH from its defined Eastern Finnish catchment population. On the other hand, only three patients with confirmed unruptured or ruptured IAs were found in the nationwide cohort of 1,410 NF1 patients. In our cohorts we found no evidence that NF1 disease is associated with IA disease, suggested by previous studies (Tables 4 and 5) and literature reviews.[14]

Table 4 NF1 cohorts with intracranial aneurysms

Author	Country	Type of study	No. of NF1 patients (No. of patients with imaging)	Mean age ± SD	Imaging and diagnosis of cerebrovascular abnormalities	No. of IA patients	No. of patients with other cerebrovascular malformations
Conway et al.[28] (2001)	USA	Retrospective	25	30 (at the time of death)	IA diagnosis based on autopsy reports	0	N/A
Rosser et al.[24] (2005)	USA	Retrospective	353 (316)	7.3 (at the diagnosis of vasculopathy)	MRI/MRA. MRI as a routine screening	1	7
Schievink et al.[26] (2005)	USA	Retrospective	39 (22)	30.4 ± 17.6	MRI. Imaging for clinical indication.	2	N/A
Cairns et al.[25] (2008)	Australia	Retrospective	698 (144)	N/A (< 18 years)	MRI/MRA/DSA. Imaging for clinical indication	0	7
Rea et al.[283] (2009)	Australia	Retrospective	419 (266)	N/A (< 18 years)	MRI/MRA. Imaging for clinical indication	1	17
Kaas et al.[284] (2013)	USA	Retrospective	181 (80)	12.2 ± 0.4	MRI/MRA/DSA. Imaging for clinical indication.	0	12
Ghosh et al.[285] (2013)	USA	Retrospective	398 (312)	11.7 ± 7.3 (at the diagnosis of vasculopathy)	MRI/MRA. Imaging for clinical indication.	0	15
Bekiesińska-Figatowska et al.[286] (2013)	Poland	Retrospective	(37)	6.6	MRA. Imaging for clinical indication	0	1
Kim et al.[29] (2016)	USA	Retrospective	(47)	38.3	MRA/CTA/DSA. Imaging for clinical indication	5	N/A

Table 5 NF1 patients with intracranial aneurysms

Author	Country	Age	Intracranial aneurysm	Presenting symptom	Sex
Patil et al.[208] (2015)	India	22	N/A	SAH	M
Conforti et al.[209] (2014)	Italy	22	ICA (fusiform)	Tolosa-Hunt syndrome	M
González-Tortosa et al.[210] (2011)	Spain	23	ICA	Diploic haematoma	F
You et al.[211] (2011)	Korea	17	MCA (saccular), extracranial ICA	–	M
Ellis et al.[212] (2011)	Canada	9	MCA (saccular)	ICH	F
Oderich et al.[27] (2007)	USA	Case 1: 50	ICA bilaterally	Asymptomatic	F
		Case 2: 20	ICA	Asymptomatic	F
		Case 3: 43	MCA, extracranial aneurysms	Asymptomatic	F
		Case 4: 74	ICA bilaterally, basilar artery, extracranial aneurysms	Asymptomatic	M
		Case 5: 43	ICA, MCA, extracranial aneurysms	SAH	F
Baldauf et al.[213] (2005)	Germany	34	ACA (saccular)	SAH	F
Mitsui et al.[214] (2001)	Japan	49	Basilar (fusiform)	Lateral medullary syndrome	M
Zhao and Han[215] (1998)	China	55	ICA (saccular)	SAH	F

Our results indicate that NF1 is not associated with elevated incidence of subarachnoid haemorrhage. However, our data does not make it possible to draw strong conclusions of the impact of NF1 on unruptured IA prevalence. The incidence of NF1 derived from the Finnish hospital registers is 1 per 2,000 live births.[201] Due to increased mortality associated with NF1, the overall prevalence of NF1 is considerably less than the birth incidence. NF1 patients have a shortened lifespan: their mean age at death is 52 years in Finland.[201] Pöyhönen et al. have estimated the prevalence of NF1 in different age groups in Northern Finnish population.[287] The observed prevalence varied by age, diminishing from the peak prevalence of about 1/3,000 in the age group 10–19 years to 1/10,000 in the age group 60–69, with the overall prevalence of 1/4,436. Evans et al. reported a similar prevalence estimate of 1/4,560.[288] Consequently, without any association between NF1 and IAs, one IA patient with NF1 would be expected–and was found–in the Kuopio IA Database.

Almost all unruptured IA cases are incidental findings in neuroimaging for other reasons and few are large enough to cause neurological symptoms by compression.[47] Only one unruptured IA, detected at autopsy, was observed in the NF1 cohort, even though many of the NF1 patients undergo MRI neuroimaging to rule out intracranial tumours. On the other hand, cranial MRI scans of NF1 patients are often obtained far earlier than IAs would be usually diagnosable. Furthermore, the patients of the NF1 register were not subject to a routine autopsy. There were two confirmed aneurysmal SAH cases among the 1,410 NF1 patients as reconstructed from the national registry data of diagnoses; two per 1,410 is well in line with the lifetime risk of aSAH in the Finnish population, with an estimated annual incidence of 9 per 100,000.[289] In addition, the occurrence of aSAH was not different between the NF1 patients and their matched controls. Consequently, aSAH does not seem to be overrepresented among NF1 patients either.

NF1 is a tumour suppressor gene whose protein product neurofibromin interacts with the RAS signalling by facilitating the inactivation of the pathway.[202] Since neurofibromin is expressed in the endothelium, localized loss of heterozygosity or haploinsufficiency of *NF1* could lead to excessive intimal thickening of the arterial wall.[290] Stenotic lesions of NF1 patients can be caused by intimal proliferation and fibromuscular dysplasia[291], but although unruptured IA walls often resemble intimal thickening, the initiation of aneurysm formation is characterized by loss of smooth muscle cells and elastic laminas.[84] NF1 is reported to associate with hypertension, an established risk factor for the IA disease.[47,292]

Previous data on possible association between NF1 and IA are based on case reports and small patient series[26,27,29,209-215,286], and have also been contested (Tables 4 and 5).[28] In a retrospective administrative database study from the USA, there were 28 (0.17%) SAH cases among 16,918 NF1 patients over 18 years, which is within the range of SAH incidence in general population as well as our NF1 cohort.[30]

Our study has several strengths. Kuopio IA Database reliably reflects the Eastern Finnish IA disease, and the initial screening of IA patients for possible NF1 was conducted with a large array of diagnoses. Furthermore, the 19,644 first-degree

relatives of the IA patients were reviewed using the national registry data for NF1 as well. Similarly, the NF1 database includes all diagnosed NF1 patients in Finland and their diagnoses have been carefully verified from individual patient records. The data quality of the Finnish national health registers has been shown to be very good.[293]

This study has some limitations. It is theoretically possible that there are more than one NF1 patients among the 4,543 IA patients in Kuopio IA Database. The database contains all IA patients admitted to KUH since 1980. The NIH criteria for the diagnosis of NF1 were established in 1987[22] and even after that there may have been NF1 patients who remained undiagnosed. Three IA patients had relatives with NF1 and considering the high penetrance of NF1, subclinical presentation of the disorder cannot be definitely excluded. NF1 cohort was not screened angiographically for the purpose of this study to rule out intracranial vascular malformations and consequently unruptured intracranial aneurysms may have remained unnoticed. We were unable to analyse the number of angiographical screenings the NF1 patients underwent based on our register data. The medical records of the patients of the NF1 register were not analysed to quantify the number of angiographical screenings these patients underwent. These factors may cause a bias and strong conclusions on the impact of NF1 to unruptured IA incidence cannot be drawn without additional studies. On the other hand, we were able to satisfactorily confirm or exclude aneurysms in all NF1 patients with SAH.

4.5 CONCLUSIONS

In conclusion, on the basis of two large Finnish population-based cohorts, 4,543 IA patients and their 19,644 first-degree relatives, as well as the nationwide population-based cohort of 1410 NF1 patients and their 14,030 matched controls, there is now evidence that NF1 does not predispose to subarachnoid haemorrhage. No evidence for an association between NF1 and unruptured IAs was found. However, further studies are required to confirm that there is no association between NF1 and unruptured IAs.

5 SACCULAR INTRACRANIAL ANEURYSMS IN CHILDREN WHEN BOTH PARENTS ARE SPORADIC OR FAMILIAL CARRIERS OF SACCULAR INTRACRANIAL ANEURYSMS

5.1 INTRODUCTION

Aneurysmal subarachnoid haemorrhage, almost always from saccular pouches formed in the forks of intracranial extracerebral arteries, is the third-most frequent form of stroke and affects working age population with a general incidence of about 9/100,000.[52,141,142] Some 3% of general population develops IA disease, but most IAs are too small to cause neurological symptoms, do not rupture, and go unnoticed during life.[9,20]

The IA disease is affected by age, female gender, smoking, hypertension, and, rarely, (1%) autosomal dominant polycystic kidney disease (ADPKD).[9,10] Like many other complex traits, the IA disease also clusters in families,[9,12-14] but currently known genomic variants explain only a fraction of the IA heritability.[16] Approximately 10–20% of IA patients belong to an IA family.[13,15] In many complex diseases, such as type 2 diabetes, the risk in the offspring is significantly increased when both parents carry the disease (Table 6).[19] With a prevalence of 3%,[20] couples in which both spouses are IA patients should be unusual but not exceedingly rare (up to 9/1,000) in general population. It is not known whether children born to parents concordant for intracranial aneurysms are at increased risk to IA disease or SAH.

Table 6 Literature review for familial predisposition to major risk factors for the complex sIA disease. sIA, saccular intracranial aneurysm; HR, hazard ratio; N/A, not applicable

	Concordance in twins		Offspring of affected parents	
sIA risk factors	**Dizygotic**	**Monozygotic**	**One parent**	**Both parents**
Hypertension[17,294]	41.6%	58.7%	HR 2.04 (95% CI 1.18 to 3.54)	HR 3.45 (95% CI 1.93 to 6.14)

Smoking[113,295,296]	25–34%	39–65%	OR 1.62 (95% CI 1.49 to 1.76)	OR 2.73 (95% CI 2.28 to 3.28)
Alcohol abuse[297]	13.3% females 31.5% males	33.2% females 56.1% males	N/A	N/A
Two unrelated complex diseases				
Type 1 diabetes[18,298]	4.8%	23.1%	0.8%	10.9%
Type 2 diabetes[19,298]	16.2%	33.9%	OR 3.5 (95% CI 2.3–5.2)	OR 6.1 (95% CI 2.9–13.0)

Our aim was to identify the families in which both parents carried a diagnosed IA disease and to study the propagation of the IA disease and hypertension in these families using the Kuopio IA Database and the Finnish national registries. We also reviewed the literature for illustrated IA pedigrees and couples concordant for IA disease in those pedigrees.

5.2 MATERIALS AND METHODS

The Kuopio Intracranial Aneurysm Patient and Family Database (www.kuopioneurosurgery.fi) contains all IA patients admitted to the Kuopio University Hospital (KUH) from a defined catchment population.[13] The clinical data of the 4,411 IA patients (620 familial and 3,780 sporadic patients) and their 46,021 relatives have been imported from the Finnish nationwide registries, including the hospital diagnoses, use of prescribed medicines, and causes of death.[42,45,47,49,299] The genealogy of the verified IA patients has been extensively mapped through parish records up to the 17th century. In addition, we searched the literature for illustrated family trees containing couples concordant for intracranial aneurysms.

5.2.1 KUH catchment population

KUH Neurosurgery has solely provided full-time acute and elective neurosurgical services for the KUH catchment population in Eastern Finland since 1977. Between 1980 and 2015, the geographic area did not change, the population decreased from 882,671 to 815,021, the median age increased from 37 to 42 years in men and from 40 to 45 years in women, while the percentage of men remained at 49%.[13,282]

5.2.2 Kuopio Intracranial Aneurysm Patient and Family Database

The Database includes all cases of unruptured and ruptured intracranial aneurysm patients admitted to KUH since 1980 for angiography and treatment, unless moribund or very aged. The database has been prospective since 1990. The database

is administrated by a full-time nurse coordinator who interviews all new patients and codes this information, including family history, and the clinical data from hospital periods and follow-up visits into an extensive list of variables. The medicine reimbursement statistics, other hospital diagnoses, and causes of death have been imported from the Finnish national registries. First- and second-degree relatives to the IA patient were identified using the personal identity codes, and their clinical data were likewise obtained. The Finnish electronic hospital diagnosis registry (Care Register for Health Care HILMO, managed by the Finnish Institution for Health and Welfare), which was cross-linked with the Kuopio IA Database, covers all secondary and tertiary centres in Finland and includes all medical specialties. Patient records of the identified parents and their children were obtained for further review. The criterion for familial IA disease was at least 2 affected first-degree relatives. The familiality of the disease of the parents was determined on the basis of their own parents and siblings. Hypertension was defined as 1) diagnosis of hypertension in the hospital discharger register or in the aneurysm database or 2) prescribed antihypertensive medications. The general limit for diagnosis of hypertension has been ≥140/≥90 mmHg during the period of time covered by the study.

5.2.3 Genealogy

Children with two IA carrying parents were identified using the information from the Finnish population register. The Finnish population register was established in 1969 and uses unique personal identification codes to register the demographic status and kinship information of all Finnish residents. In addition, all new IA patients were routinely interviewed for information suggesting familial disease and identified IA families were more thoroughly investigated by professional genealogists who researched parish records to expand the breadth and depth of the pedigrees and to assess consanguinity in maternal and paternal pedigrees and interconnections between the different families. Parish records enable identification of older familial relationships, including data from several previous centuries.

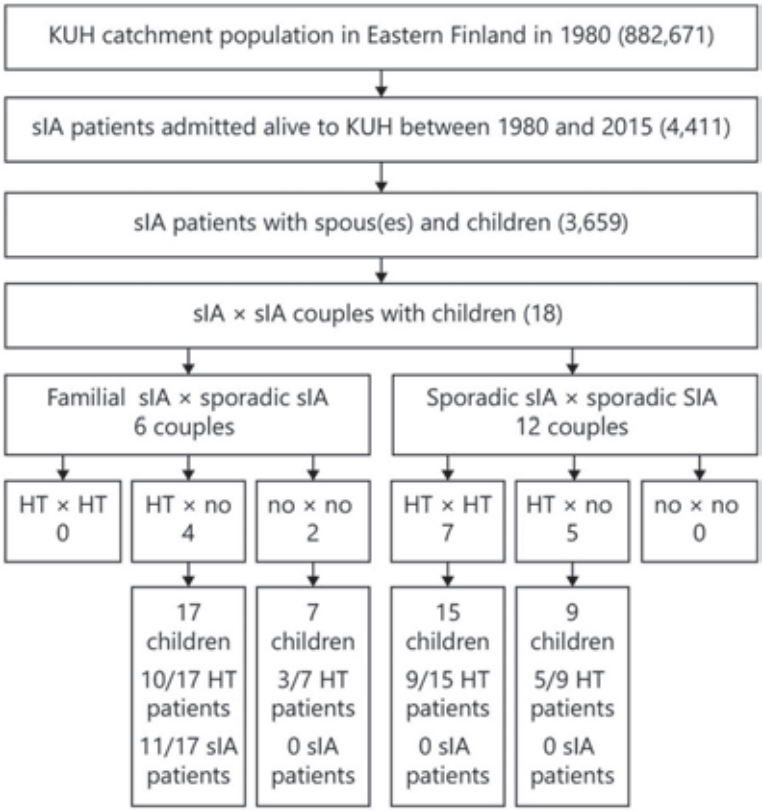

Figure 6 Biparental saccular intracranial aneurysm (sIA) disease families. Identification of 18 couples concordant for sIA disease with 48 children among the 4,411 sIA patients admitted alive to the Kuopio University Hospital (KUH) from its Eastern Finnish catchment population between 1980 and 2015. Couples with or without hypertension (HT) are indicated. sIA × sIA, couple concordant for sIA disease; HT × HT, couple concordant for hypertension; no × no, normotensive couple.

5.2.4 Literature review for illustrated IA family trees

Pubmed was searched in 6/2017 for illustrated IA pedigrees, using the terms "aneurysm* AND (intracranial OR cerebral OR brain OR CNS OR "central nervous system" OR subarachnoid) AND (family OR families OR familial OR pedigree* OR kindred* OR linkage)". We reviewed all 667 articles published in English between 1995 and 2016, a period of noninvasive IA imaging by CT and MR, for (a) illustrated pedigrees and (b) couples concordant for saccular IAs in those pedigrees. Some family trees seemed duplicates but were not separable by the available data, and some did not differentiate saccular IAs from other types of IAs.

5.2.5 Ethical approvals

The Kuopio IA Patient and Family Database has been approved by the Ethical Committee of the KUH, the Finnish Ministry of Social Affairs and Health, and the National Institute for Health and Welfare. Written informed consent was obtained from all the IA patients registered to the Database.

5.3 RESULTS

The Kuopio IA Database contains 4,411 saccular IA patients, 1,356 unruptured IA patients and 3,055 patients with aneurysmal SAH with the first IA diagnosis between 1980 and 2015 (Figure 6). The 53 IA patients with known ADPKD[10] were excluded from the present analysis. We identified, using the Finnish identity codes, 46,021 relatives to the 4,411 IA patients. A total of 3,659 IA patients had had one or more children with a median age of 25 years (quartiles 22 and 28 years) at the birth of the first child.

We identified 18 couples with both parents carrying the IA disease who had children (Figure 6, Table 7). There were 12 couples of two sporadic IA patients and six couples of a familial IA patient and a sporadic IA patient, but no couples of two familial IA patients. The number of couples concordant for SAH in the respective groups was six and two. Characteristics of the 18 couples and their 48 children are shown in Table 7.

The pedigrees of the identified families were reconstructed using the parish records to the depth of two to seven generations preceding the index couple, the six pedigrees with a familial IA parent exemplified in Figures 7 and 8. No consanguinity was found between the maternal and paternal lines of the 18 index couples.

Table 7 Penetrance of the sIA disease in the 48 children of the 18 couples in which both spouses were sIA carriers

	Both parents carrying sIA disease among the 3,659 sIA patients with one or more children										**sIA patients (n=4,411)**	
	Familial* sIA x sporadic sIA (6 couples)						Sporadic sIA x sporadic sIA (12 couples)				Unruptured (n=1,356) 271 (20%) familial	Ruptured (n=3,055) 323 (11%) familial
	12 sIA parents		24 children				24 sIA parents		All 24 children unaffected			
			11 affected		13 unaffected							
	8 SAH	4 UsIA	3 SAH	8 UsIA	6 negative MRA CTA	7 no MRA CTA	16 SAH	8 UsIA	5 negative MRA CTA	19 no MRA CTA		
Median age at first sIA diagnosis	54	65	37	43	–	–	56	67	–	–	57	52
Median age at last negative MRA or CTA	–	–	–	–	36	–	–	–	48	–	–	–
Median age at last follow-up					59	57			50	51		
Multiple sIAs (2 or more)	1/8	1/4	1/3	4/8	0	–	5 /16	2/8	0	–	392 (29%)	831 (27%)
Hypertension**	See the flowchart in Figure 6										1,040/1,286 (81%)*	1,203/1,679 (72%)*

* Each of the six familial sIA patients (parents) had at least two affected first-degree relatives. ** Hypertension in the 2,965 patients with first sIA diagnosis between 1995 and 2015. Hypertension was defined as (1) diagnosis of hypertension by a physician or (2) prescribed antihypertensive medications

5.3.1 IA disease in the 24 children of the 12 sporadic-sporadic couples

Of the 24 children to the 12 sporadic-sporadic couples, none had been diagnosed with the IA disease or SAH until a median age of 51 years (quartiles 43 and 55 years). In 19 cases, MRA or CTA screening had not been performed (Table 7). Drug-treated hypertension was carried in seven couples by both parents and in five couples by one parent (Figure 6). Of the 24 children, 14 have been diagnosed with hypertension.

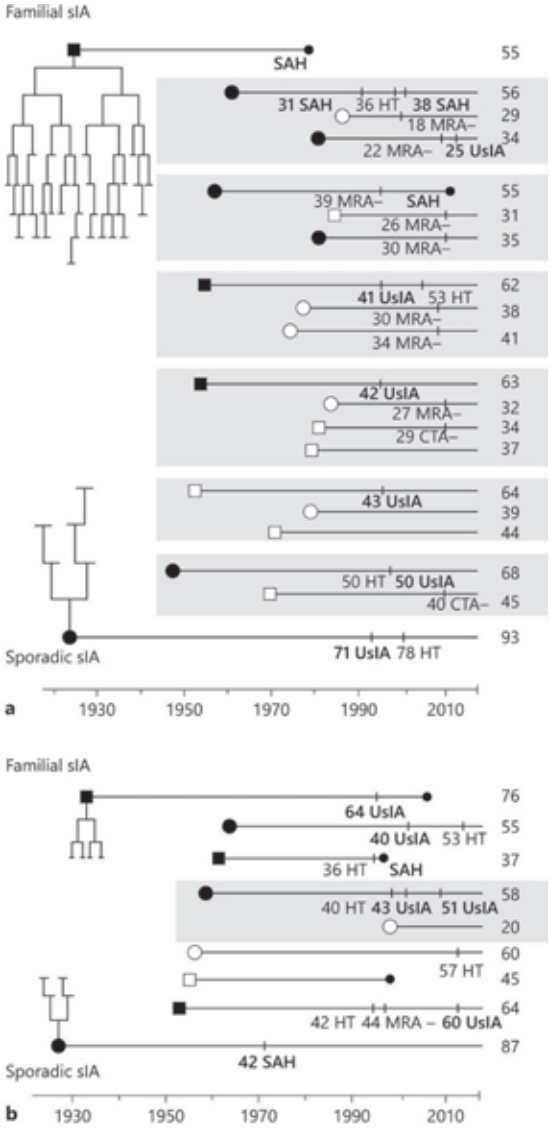

Figure 7 The clinical penetrance of saccular intracranial aneurysm (sIA) disease in 2 of the 6 families where one parent is a familial sIA patient, with 2 or more sIA patients in the pedigree, and the other parent is a sporadic sIA patient, with no diagnosed sIA carriers in the pedigree. The illustrated 2 families (a, b) presented with high clinical penetrance in the offspring. The calendric lifelines from the birth to the death (age shown) or the last follow-up (age shown) are presented. The large black symbols denote sIA patients and the white ones unaffected family members. The gray rectangular areas denote each child with children of each familial-sporadic couple. The traditional pedigree lines from the 2 couples to their children and grandchildren were omitted for the sake of visual clarity. The 6 pedigrees were constructed using the Finnish personal identity codes and the available parish records to exclude consanguinity in previous generations between the paternal and the maternal pedigrees (ancestry of the parents shown on the left side of each family tree). The familiality of the disease of the parents was determined on the basis of their parents and siblings (not shown). SAH, subarachnoid haemorrhage; UsIA, unruptured sIA; HT, diagnosed hypertension; MRA, magnetic resonance angiography; MRA–, no sIA disease in MRA; CTA, computed tomography angiography; CTA–, no sIA disease in CTA.

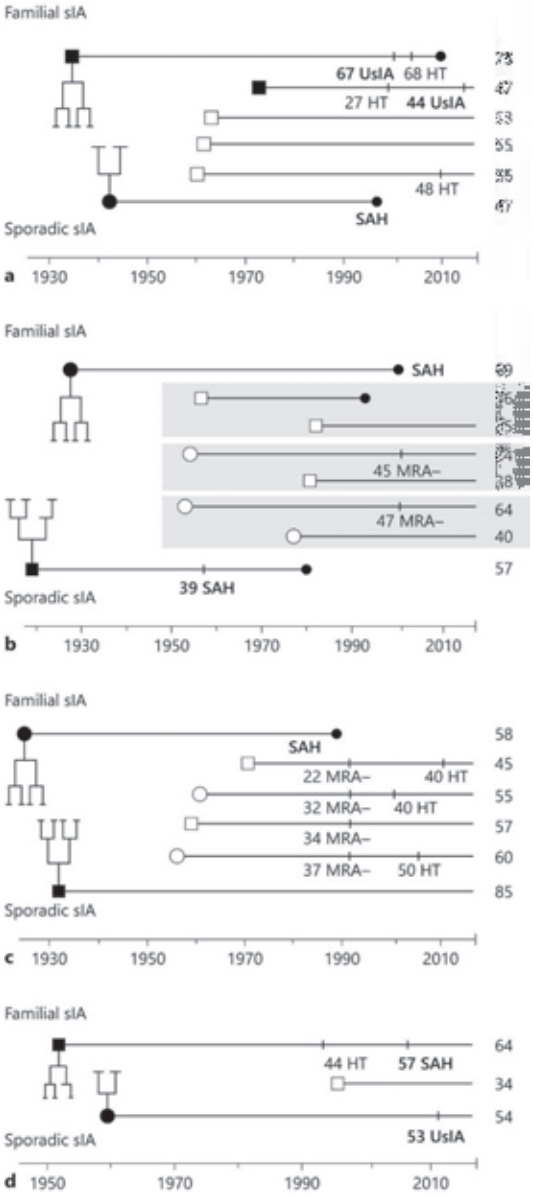

Figure 8 The clinical penetrance of saccular intracranial aneurysm (sIA) disease in 4 of the 6 families where one parent is a familial sIA patient, with 2 or more sIA patients in the pedigree, and the other parent is a sporadic sIA patient, with no diagnosed sIA carriers in the pedigree. The illustrated families (a–d) presented with low clinical penetrance in the offspring. The calendric lifelines from the birth to the death (age shown) or the last follow-up (age shown) are presented. The large black symbols denote sIA patients and the white ones unaffected family members. The gray rectangular areas denote each child with children of each familial-sporadic couple. The traditional pedigree lines from the 4 couples to their children and grandchildren were omitted for the sake of visual clarity. The 6 pedigrees were constructed using the Finnish personal identity codes and the available parish records to exclude consanguinity in previous generations between the paternal and the maternal pedigrees (ancestry of the parents shown on the left side of each family tree). The familiality of the disease of the parents was determined on the basis of their parents and siblings (not shown). SAH, subarachnoid haemorrhage; UsIA, unruptured sIA; HT, diagnosed hypertension; MRA, magnetic resonance angiography; MRA–, no sIA disease in MRA; CTA, computed tomography angiography; CTA–, no sIA disease in CTA.

5.3.2 IA disease in the 24 children of the 6 familial-sporadic couples

Of the 24 children to the six familial-sporadic couples, 11 had been diagnosed with the IA disease at a median age of 57 years (quartiles 49 and 63 years), three presenting with SAH and eight with UIA (Figures 6 and 7). Four couples were concordant for drug-treated hypertension, and two couples had one parent diagnosed with hypertension. A total of 13 children had been diagnosed with hypertension. Of the six pedigrees, two (Families A and B in Figure 7) stand out with a high prevalence of the IA disease in the offspring. Of the six children, six were affected in the family A

and four out of six children were affected in the family B. MRA or CTA screening had been performed in six of the unaffected cases (Table 7, Figures 7 and 8).

5.3.3 Literature review

We reviewed 424 illustrated intracranial aneurysm family trees in 667 articles published between 1995 and 2016. We identified only two families in which both parents were IA patients, one from Greenland,[300] and one in our previous article[301] (Family A in Figure 7).

5.4 DISCUSSION

In the present study, we perused the Kuopio IA Patient and Family Database, containing 3,659 IA patients with one or more children, and their clinical lifelines constructed from the birth to the death or the last follow-up, using all clinical data from the national registries. Assuming a general prevalence of 1–3% for the IA disease,[9,14,20] the 3,659 couples would include some 37 to 110 couples concordant for a diagnosed or undiagnosed IA disease. However, we identified only 18 such couples (0.4%), six familial-sporadic couples and 12 sporadic-sporadic couples with altogether 48 children. All 36 IA parents had had their first child before their IA diagnosis.

Clinical penetrance of the complex IA disease, whether unruptured or ruptured, from IA carrying parents to their offspring has not been comprehensively studied according to our literature review. In the present study, we hypothesized that penetrance would be increased when both parents carry the IA disease, similar to other complex diseases such diabetes type 2 (Table 6). The two most important modifiable risk factors to the complex IA disease, whether sporadic or familial, hypertension and smoking, are themselves more common in children with two affected parents and show significant concordance in monozygotic twins (Table 6).[35,36] Hypertension increases the hazard of developing UIAs approximately two-fold in patients with previous aneurysmal SAH and smoking three- to six-fold.[46,92,302] In a large, population-based cohort, hypertension increased the hazard for SAH by a factor of 2.5, and smoking increased the hazard up to three-fold, and alcohol abuse up to two-fold.[303] In the previously published 424 illustrated intracranial aneurysm family trees, we found only two couples concordant for intracranial aneurysms.[300,301]

Biparental sporadic exposure does not seem to increase the risk of a clinically diagnosed IA disease in the offspring whereas biparental sporadic-familial exposure seems to increase the risk. However, it is so far not clear whether the sporadic parent brought any additional effect on the penetrance. Families in which both parents had had SAH were more common in the sporadic-sporadic group. It is notable that none of their children had had SAH, a disease that could be confirmed or excluded more reliably than UIAs in the study population, during the follow-up period.

In our study population, hypertension was more prevalent among the sporadic-sporadic couples than among the familial-sporadic couples (Figure 6, Table 7). It is notable that even the 15 children to the seven sporadic-sporadic couples that were concordant for diagnosed hypertension, did not have a diagnosed IA disease.

Using the parish records, genealogy of the IA pedigrees in our database is traceable up to seven generations before the index IA patient. We found no consanguinity in the identifiable generations in the family trees of the present 18 couples, including the most penetrant family (Family A, Figure 7).

Our study has limitations. A thorough analysis of clinical penetrance from IA parents to their offspring requires very long follow-up times because the diagnosis of the IA disease is usually made at 50 to 60 years, and very rarely before 30 years of age.[9,50] None of the 24 children of the 12 sporadic couples had a clinical diagnosis of the IA disease, but some might be or become IA carriers as 19 of them had not had CTA or MRA follow-up (Table 7). Among the 24 children of the six familial-sporadic couples, our IA family screening program had been applied variably (Table 7, Figure 7, Figure 8). A more reliable assessment of the effect the diseased state of both parents has on the UIA status of the offspring would require a systematic screening. We found no cases of SAH or UIAs in the children of the sporadic-sporadic couples. However, the median age of the offspring at the end of the follow-up, 51, is less than that of their parents at the time of the diagnosis of SAH or UIA (56 and 67 respectively). As paternity is not routinely confirmed by e.g. serological or DNA testing, we cannot exclude the possibility of misattributed biological relationships.

There were also several strengths. The Finnish health care system is universal and publicly funded, reducing bias in population-based disease databases. Neurosurgery of the Kuopio University Hospital (KUH) has solely provided full-time acute and elective neurosurgical services for the Eastern Finnish catchment population, including unruptured and aneurysmal SAH patients. The Kuopio IA Patient and Family Database, using the personal identity codes, has incorporated clinical data for both the IA patients and their relatives from the national registries. The diagnosis of aneurysmal SAH, a medical and neurosurgical emergency, could thus be assessed reliably over a long period of time in the studied population.

The Finnish population, including Eastern Finland, is one of the most thoroughly characterized genetic isolates.[16] The small size of the founder population, bottleneck effects and genetic drift have led to enrichment for rare and low frequency variants that are almost absent in other European populations and some variants rare elsewhere are increased in frequency.[16] Our previous genotyping of 858 Finnish IA patients and 4,048 controls, compared to 717 Dutch cases and 3,004 controls, suggested five loci associating to the IA disease in Finland.[16] These variants, at present, do not provide a reliable polygenic risk score to predict individual IA carriership. We now hypothesize that increased penetration of IA disease in our large Eastern Finnish IA pedigrees with consanguinity, as well as in the present familial-sporadic IA couples, would be associated to rare or low-frequency variants in the Eastern Finnish population. Exomic sequencing of such cases is currently in progress.

5.5 CONCLUSIONS

Couples concordant for IA disease are uncommon but not rare. They have children before their own IA diagnosis at the age of 50 to 60 years. Biparental sporadic exposure does not seem to increase the risk of a clinically diagnosed IA disease in the offspring whereas IAs were substantially more common in families with biparental sporadic-familial exposure. Importantly, no cases of SAH were diagnosed in the offspring with biparental sporadic-sporadic exposure to SAH. In general, the mechanisms of the increased penetrance in the familial IA disease warrant further analysis.[9,14] In clinical practice, detailed maternal and paternal family trees should be created for all couples concordant for IA disease to find out whether any relative is an IA disease carrier, suggesting an IA family.

6 ASSOCIATION OF INTRACRANIAL ANEURYSMS WITH AORTIC ANEURYSMS IN 125 PATIENTS WITH FUSIFORM AND 4,253 PATIENTS WITH SACCULAR INTRACRANIAL ANEURYSMS AND THEIR FAMILY MEMBERS AND POPULATION CONTROLS

6.1 INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH), at an incidence of 7.9 per 100 000 and in an average age of 50 to 60 years[6], is a devastating form of stroke: 20% of aSAH patients die instantly[54] and up to 30% within 12 months.[42] In most cases, the cause is rupture of a saccular intracranial aneurysm (sIA), formed during life in some 3% of general population.[20] Risk factors for sIA include age, female gender, smoking, hypertension, sIA family history, and polycystic kidney disease.[9] Fusiform IAs (fIAs), like aortic aneurysms (AA), are dilatations of arterial segments[8,165]: fIAs are uncommon, and remain poorly characterised and difficult to treat.[165]

Aortic aneurysms (AA) are increasingly prevalent amongst aging population especially in aging, smoking, hypertensive men.[31-33] The incidence varies from 6–10.4 per 100 000 for thoracic aortic aneurysms (TAA)[31] to 0.89–176.08 per 100 000 for abdominal aortic aneurysms (AAA), the prevalence increasing steeply towards the most aged groups.[222] Familial background precedes 20% of thoracic aortic aneurysms (TAA) and positive family history is a known risk factor for abdominal aortic aneurysm (AAA).[31-33]

Increased prevalence of IA in AA patients, as well as AA in IA patients, has been suggested in several studies.[34-41] However, these cohorts did not contain patients and

controls from defined catchment populations and, in most cases, fIAs were not distinguished from sIAs.

We analysed, in retrospect, the characteristics of the 125 fIA patients with 134 fIAs as compared to the 4,253 sIA patients with 6,097 sIAs from a defined population in the Kuopio Intracranial Aneurysm Patient and Family Database, which comprises all the IA patients of Eastern Finland diagnosed or treated in Kuopio University Hospital (KUH) since 1980. We studied the prevalence of AA in these fIA patients and sIA patients and in their first-degree relatives, and in the patients' matched population controls, using the Finnish national clinical registries. Hypothesising that fIAs and AAs, both fusiform in shape, share genomic risk factors, we systematically reviewed the literature for family trees containing IA and AA patients and for patient cohorts with patients with both IA and AA. Finally, we sequenced 33 fIA patients with an aortic gene panel of 37 AA-related genes.

6.2 METHODS

Data that support the findings of this study are available to qualified researchers who meet the criteria provided by the board of the Kuopio Intracranial Aneurysm Patient and Family database (http://kuopioneurosurgery.fi). The Finnish National Institute for Health and Welfare provides data for all researchers who meet the criteria set by the Institute.

6.2.1 KUH catchment population

KUH Neurosurgery has been sole provider of full-time acute and elective neurosurgical services for the KUH catchment population in Eastern Finland since 1977. Between 1980 and 2015, the geographic area of the KUH hospital districts did not change, the population decreased from 882,671 to 815,021, the median age increased from 37 to 42 years in men and from 40 to 45 years in women whereas the proportion of men has remained at 49%.[13,304]

6.2.2 Kuopio IA Patient and Family Database

The database includes all cases of unruptured and ruptured IA patients admitted to KUH since 1980 for angiography and treatment, unless moribund or very aged. The database has been prospective since 1990. The database is administrated by a full-time nurse coordinator who interviews all new patients and codes this information, including family history, and the clinical data from hospital periods and follow-up visits into an extensive list of variables. The criterion for familial IA disease was at least two affected first-degree relatives. The genealogy of the verified IA patients has been extensively mapped through parish records up to the 17th century.[304] The phenotype, concomitant diseases, genetics, and outcome of Eastern Finnish sIA patients have been analysed in several studies.[10,13,45,304]

6.2.3 Study population

The Kuopio IA Database includes only the patients with intracranial aneurysm(s) in four-vessel angiography (DSA, CTA or MRA), initially verified by both a neurovascular neurosurgeon and a neuroradiologist. The 125 fIA patients were agreed to carry fusiform or dolichoectatic aneurysms in a re-review by a neurosurgeon (B.R.J.) and an interventional neuroradiologist (O.T.) (Figure 9) Intracranial artery dissections were excluded. The size of the fIAs was defined as the greatest length or largest perpendicular diameter, whichever larger.

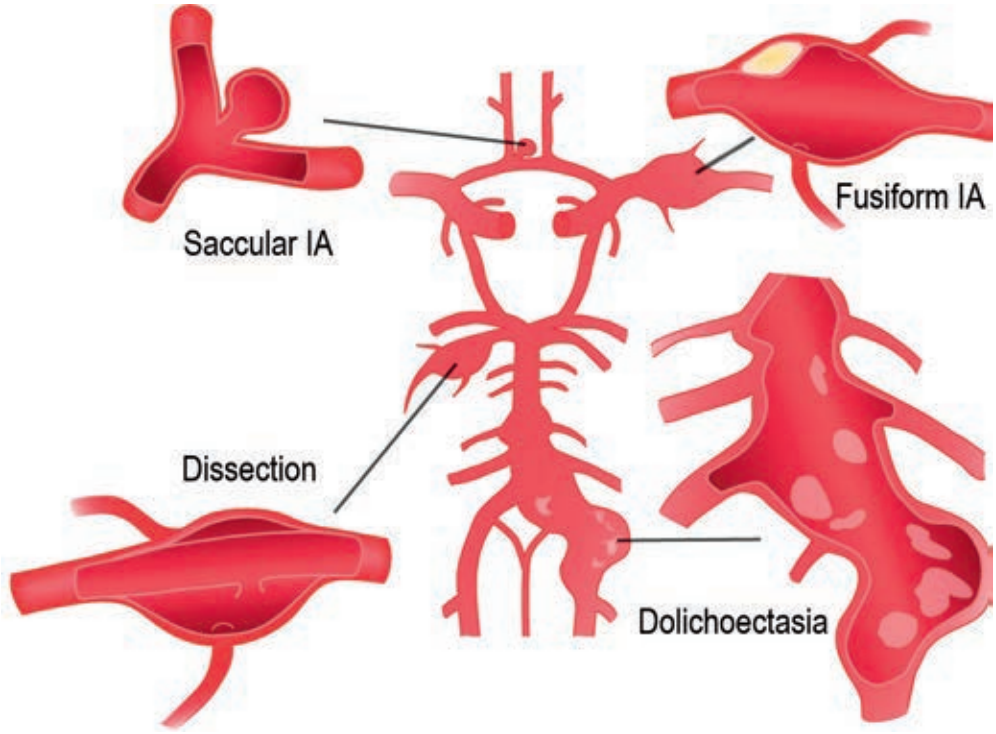

Figure 9 The major intracranial extracerebral arteries with the circle of Willis (middle). The saccular intracranial aneurysm (sIA, left upper) forms at the branching sites of the arteries, whereas the uncommon fusiform intracranial aneurysm (fIA, right upper) mainly involves the arterial trunks (see Fig. 4.). The dolichoectasia (right lower) usually involves the vertebrobasilar trunk. The acute dissection with false lumen (left lower), more frequent in the cervical arteries, is also shown. Note the atheromatous plaque of the fIA wall and the calcification of the dolichoectatic artery.

A total of 450 and 17,825 first-degree relatives were identified to the 125 fIA patients and the 4,253 sIA patients, respectively, using the personal identity codes and the Finnish Population Register Centre (Figure 10).[304,305] A total of 340 and 12,669 matched population controls were assigned to the 125 fIA patients and the 4,253 sIA patients, respectively, matched by age, gender, year and municipality at the IA diagnosis. The index date for the matching was the date of the admission for IA or

aSAH, with all controls alive at that point. Although we aimed at a 3:1 ratio (controls:patients), this ratio was not achieved in 35 fIA and 90 sIA patients.

6.2.4 Data fusion from national registries

The drugs prescribed for the patients, the family members and the controls, purchased from apothecaries, as well as the hospital diagnoses and the causes of death have been imported from the Finnish national registries.[13] The Finnish electronic hospital diagnosis registry (Care Register for Health Care HILMO, managed by the Finnish Institution for Health and Welfare), which was cross-linked with the Kuopio IA Database, covers all secondary and tertiary centres in Finland and includes all medical specialties. The hospital diagnoses from 1969 to 2014 and medication reimbursement statistics from 1995 to 2014 were available.

The prevalence of hypertension and atherosclerotic disease were investigated with both the hospital discharge register and the national medicine reimbursement statistics. Hypertension was defined as either 1) diagnosis of hypertension or hypertensive disease in the diagnosis registry or 2) use of prescribed antihypertensive medication (ATC codes C02, C03A, C04, C08 and C09). The general limit for diagnosis of hypertension has been ≥ 140/ ≥ 90 mm Hg during the time period covered by the study. Atherosclerotic disease and hyperlipidaemia were defined as either 1) diagnosis of atherosclerotic disease (peripheral atherosclerosis, atherosclerotic heart disease, atherosclerotic disease of cerebral arteries) or 2) use of prescribed lipid-lowering drugs (ATC code C10).

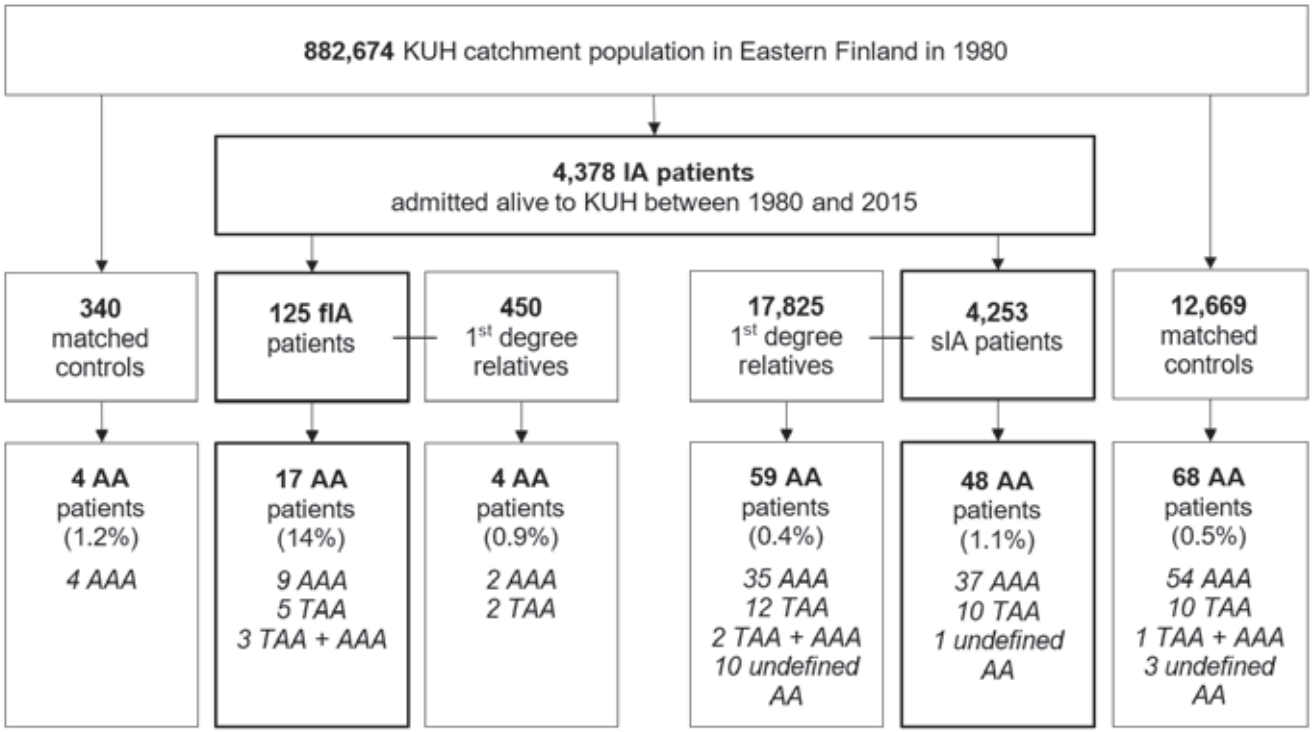

Figure 10 Flowchart of the study population: 4,378 patients with intracranial aneurysm (IA) disease admitted to the Kuopio University Hospital (KUH) with an unruptured IA or first aneurysmal subarachnoid hemorrhage (aSAH) from the Eastern Finnish catchment population from 1980 to 2015. A total of 450 and 17,825 first-degree relatives were identified to the 125 patients with fusiform IA (fIA) and the 4,253 patients with saccular IA (sIA), respectively, using the personal identity codes and the Finnish Population Register Centre. A total of 340 and 12,669 matched population controls were assigned to the 125 fIA patients and the 4,253 sIA patients, matched by age, gender, year and municipality at the IA diagnosis. In 35 fIA patients and 90 sIA patients, the 3:1 ratio was not achieved. AA, aortic aneurysm; AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysm; undefined AA, AA of undefined site.

6.2.5 Diagnosed aortic aneurysms in the study population

The diagnosed aortic aneurysms in the 4,378 IA patients and their 17,278 first-degree relatives and 13,009 population controls were obtained from the Finnish national hospital discharge register (Care Register for Health Care). The ICD-9 and ICD-10 codes for aortic dissections and aneurysm (441.0–441.9 and I71.00–I71.9.) were used. Furthermore, the chest radiographs, as well as thoracic and abdominal CT or ultrasound imaging available for 80 (64%) fIA patients were re-reviewed by a neurosurgeon (B.R.J.) and an interventional radiologist (H.M.) for presence of aortic aneurysms. The patient records of the IA patients with AA or dissection were obtained whenever possible to ascertain the diagnosis and the type of AA.

6.2.6 Genotyping with the aortic aneurysm gene panel

Of the 41 fIA patients alive 33 were available for genotyping with informed and signed consent. Four of these 33 patients were diagnosed with AA. First-degree relatives of the patients were not available for screening. Targeted sequencing was performed using OS-seq technology described earlier[306,307] using a commercial Aorta Panel consisting of 37 AA genes: *ABCC6*, *ACTA2*, *ADAMTS2*, *CBS*, *COL1A1*, *COL1A2*, *COL2A1*, *COL3A1*, *COL5A1*, *COL5A2*, *COL9A1*, *COL9A2*, *COL11A1*, *COL18A1*, *EFEMP2*, *ELN*, *ENPP1*, *FBLN5*, *FBN1*, *FBN2*, *FKBP14*, *FLNA*, *GATA5*, *MFAP5*, *MYH11*, *NOTCH1*, *PLOD1*, *SKI*, *SLC2A10*, *SLC39A13*, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2*, *TNXB*, *ZNF469* (www.blueprintgenetics.com). All protein coding exons and exon-intron boundaries (±15 bps) are covered in each targeted gene and the panel has high sensitivity to detect SNVs, small insertions and deletions up to 50 bps as well as exon level CNVs. Variant classification followed the 2015 ACMG guideline.[308]

Shortly, pathogenicity of the identified variants were assessed by considering the predicted consequence, the biochemical properties of the codon change, the degree of evolutionary conservation as well as a number of reference population databases and mutation databases such as, but not limited, to the 1000 Genomes Project, gnomAD, ClinVar and HGMD. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster were used to assist with variant classification.

6.2.7 Statistical analysis

Categorical variables were compared between groups with $\chi 2$ and Fisher's exact tests as appropriate. Continuous variables were tested with the Student's t test or Mann-Whitney U test as appropriate. As aortic aneurysms and death might share risks factors, competing risks multivariate Cox regression was performed to determine risk factors for the diagnosis of aortic aneurysms among IA patients. The variables

used in the model were sex, hypertension, any diagnosed atherosclerotic disease or prescribed lipid-lowering drug, type 2 diabetes, IA rupture status, and IA morphology. Schoenfeld residuals were used to confirm the model's assumption of proportionality. The results are expressed as subdistribution hazard ratios (SHRs) with 95% confidence intervals (CIs). Two-tailed p value <0.05 was considered significant.

Analyses were performed using IBM SPSS Statistics, version 22.0 (IBM SPSS, Armonk, NY) and the R environment for statistical computing, including cmprsk library.

6.2.8 Literature review

Two literature searches were performed in September 2018 for English articles published between 1995 and 2016, a period of non-invasive IA imaging by CT and MR. Firstly, all cohorts with concurrent IA and AA were searched with the terms: (aneurysm OR dolichoecta*) AND (aorta OR aortic OR abdominal OR thoracic) AND (intracranial OR cerebral OR cns OR brain OR subarachnoid*) AND (prevalen* OR inciden* OR epidemiology OR population). This gave 3,969 hits). All abstracts were reviewed, and the case reports and duplicates were excluded. The remaining articles were searched for cohorts that reported the angiographically identified IAs in the patients with diagnosed AA and cohorts that reported diagnosed AAs in the patients with IA. The final eight cohorts presented the proportion of IAs among the AA patients or AAs among the IA patients (Figure 11, Table 8).

Secondly, all illustrated IA family trees with co-occurrence of AA and AA family trees with co-occurrence of IA were searched with the terms: (intracranial OR cerebral OR cns OR brain OR subarachnoid*) AND (aortic OR aorta) AND aneurysm* AND (gene OR genetic* OR genome OR family OR famil* OR kindred OR generation OR hereditary OR heritable OR inherited OR phenotyp* OR mutation* OR variant* OR polymorphism OR linkage OR chromosomal). This gave 314 articles. Some family trees seemed to be duplicates but were not separable by the available data, and may consequently be counted twice, and some did not differentiate saccular IAs from other types of IAs. The final eight cohorts presented 27 family trees (Figure 12, Table 9).

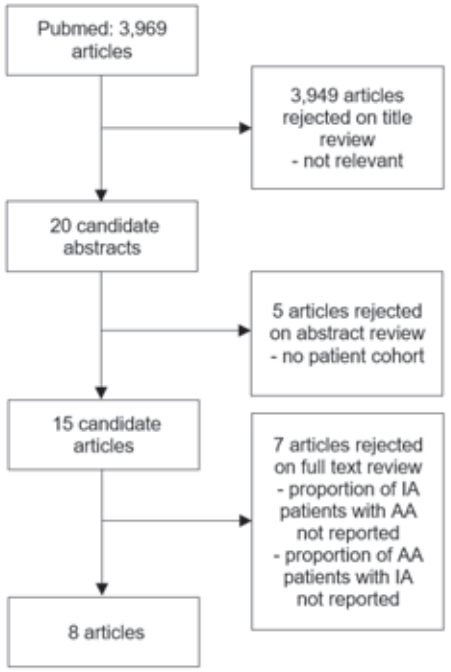

Figure 11 Literature search for patient cohorts with concurrent IA and AA

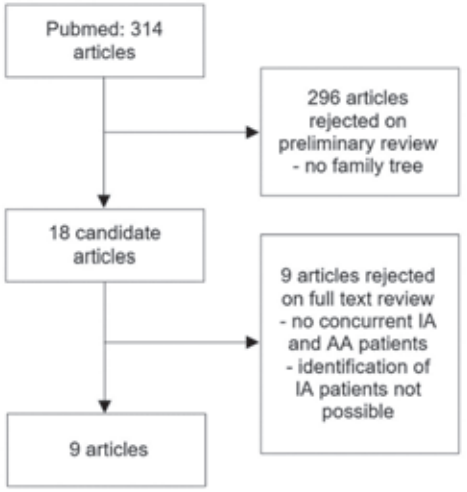

Figure 12 Literature search for family trees with both IA and AA patients

Table 8 Published relevant cohorts of patients with intracranial aneurysms (IA) and aortic aneurysms (AA).

IA patients with AAs

Reference	Number of patients	Imaging modality	Proportion of patients with both IA and AA
Flemming et al.[34] **2005**	159 patients with fIA or dolichoectasia†	Not reported	AAA 29/159 (18%) sIA 16/159 (10%)
Miyazawa et al.[35] **2007**	181 IA patients*	Abdominal ultrasound	AAA 13/181 (7%)
Goyal et al.[37] **2015**	317 IA patients*	TTE or TEE	TAA 15/317 (5%)
Brinjikji et al.[40] **2016**	139 patients with vertebrobasilar dolichoectasia† 25 with diffuse intracranial dolichoectasia†	Not reported	AAA 12/139 (14%) AAA 10/25 (63%)

AA patients with IAs

Kuzmik et al.[36] **2010**	212 TAA patients 52 retrospective and 160 prospective	MRA or CTA	IA* 9/52 (17%) and IA* 10/160 (6%)
Lee et al.[41] **2017**	133 AA patients 25 aortic dissection patients	MRA or CTA	sIA 25 and fIA 2/133 (20%) sIA 8/25 (30%)
Shin et al.[38] **2015**	660 AA patients	MRA or CTA	IA 71/660 (12%) *fIAs excluded*
Rouchaud et al.[39] **2016**	1081 AA patients	CTA or MRA or DSA	sIA 128/1081 (12%) *20 dissections or fIAs excluded*

*Fusiform (fIA) and saccular intracranial aneurysm (sIA) were not distinguished.
†Partially same patient cohort
TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; MRA, magnetic resonance angiography; CTA, computed tomography angiography; DSA, digital subtraction angiography

Table 9 Published family trees including patients with both intracranial (IA) and aortic aneurysms (AA)

	Family members	IA patients with no AA	IA patients with AA	AA patients with no IA	Implicated genes
Schievink et al.[309] 1997	19	2 IA*	1 IA* + TAA	0	
Cannon-Albright et al.[310] 2003	69	7 IA*	0	4 AA*	
Nahed et al.[311] 2005	19	2 IA*	1 IA* + TAA	0	
Kim et al.[312] 2005	28	4 IA*	0	4 AA*	
	16	3 IA*	0	3 AA*	
	24	4 IA*	0	2 AA*	
	22	3 IA*	1 IA* + AA*	1 AA*	
	25	5 IA*	0	1 AA*	
	16	1 IA*	0	10 AA*	
Regalado et al.[313,314]	19	1 IA*	1 IA* + TAA	6 TAA	
	32	1 IA*	0	7 TAA	
	8	2 sIA	0	2 TAA, 3 AAA	
	17	1 IA*	1 IA* + TAA	4 TAA, 1 AAA	
	14	4 IA*	0	3 TAA	
	10	1 IA*	1 IA* + TAA	1 TAA, 1 AAA	
	6	1IA*	0	2 TAA	
	6	1 IA*	1 IA* + TAA	2 TAA	
	19	2 sIA	0	6 TAA	
	17	2 IA*	0	2 TAA	
	13	2 sIA	0	2 TAA	
	7	1 IA*	0	2 TAA, 1 AAA	
	11	1 IA*	0	4 TAA	
	24	3 sIA	0	6 TAA	
	17	1 IA*	1 IA* + TAA	4 TAA, 1 AAA	SMAD3
Luukkonen et al.[315] 2012	20	1 IA	0	3 AA*	NTM
Bertoli-Avella et al.[316] 2015	23	0 IA	1 IA* + AA*	2 AA*	TGFB3
Mazzella et al.[317] 2017	22	1 fIA	0	5 TAA	TGFB2
Total	523	57 IA	9 IA + AA	95 AA	

6.2.9 Ethical approvals

The Kuopio IA Patient and Family Database has been approved by the Research Ethics Committee of the KUH, the Finnish Ministry of Social Affairs and Health, and the
National Institute for Health and Welfare. Written informed consent was obtained from all the IA patients registered to the Database.

6.3 RESULTS

6.3.1 Our study population

There were 125 patients with 134 fIAs and 4,253 patients with 6,097 sIAs (Figure 9, Figure 10, Table 10, Table 11). Of the 125 fIA patients, 22 (18%) carried also sIAs. For the 125 fIA patients, there were 450 first-degree relatives and 340 matched population controls, and for the 4,253 sIA patients 17,825 first-degree relatives and 12,669 matched controls (Figure 10, Table 10).

Table 10 Characteristics of the 4,378 patients with intracranial aneurysms

Variables for 4,378 IA patients from 1980 to 2015	125 fusiform IA patients including 22 fIA patients with concomitant sIAs			450 1st degree relatives to the fIA patients	340 matched controls to the fIA patients	4,253 saccular IA patients with no fIAs			17,825 1st degree relatives to the sIA patients	12,669 matched controls to the sIA patients	P value – total fIA versus total sIA*
	Unruptured fIA n=93 (64%)	Ruptured fIA n=32 (26%)	Total fIA n=125	0 fIA 1 sIA	0 fIA 1 sIA	Unruptured sIA n=1,330 (31%)	Ruptured sIA n=2,923 (69%)	Total sIA n=4,253	0 fIA 224 sIA (76 aSAH)	0 fIA 58 sIA (33 aSAH)	<0.0005
Median age at IA diagnosis, y (25 and 75 percentiles)	66 (57-72)	59 (48-73)	64 (55-72)	47 at sIA	75 at sIA	57 (48-66)	52 (43-62)	54 (45-63)	47 (42-54) at sIA	56 (52-73) at sIA	<0.0005
Presentation *Incidental *Symptomatic *sIA family screening	64 (69%) 29 (31%) –	–	–	–	–	1164 (88%) 54 (4%) 112 (8%)	–	–	–	–	<0.0005
Females, n (%)	39 (42%)	21 (66%)	60 (48%)	222 (49%)	160 (47%)	754 (57%)	1.598 (55%)	2.352 (55%)	8,706 (49%)	7,029 (55%)	0.106
sIA family, n (%)	5 (5%)	2 (6%)	7 (5.7%)	–	–	259 (20%)	314 (11%)	573 (14%)	–	–	0.007
Concomitant sIA, n (%)	–	–	22 sIA (18%)	–	–	–	–	–	–	–	
Multiple fIAs (≥2), n (%)	7 (8%)	1 (3%)	8 (6%)	–	–	–	–	–	–	–	
Multiple sIAs (≥2), n (%)	9 (10%)	0 (0%)	9 (7%)	–	–	380 (29%)	811 (28%)	1.191 (28%)	–	–	
AAA total *ruptured*	9 (10%) *2 (2%)*	–	9 (7%) *2 (2%)*	2 (0.4%) –	4 (0.6%) –	24 (2%) *2 (0.2%)*	13 (0.4%) *6 (0.2%)*	37 (1%) *8 (0.2%)*	35 (0.2%) *11 (0.1%)*	54 (0.4%) *12 (0.1%)*	<0.0005

Confirmed TAA total ***ruptured***	1 (1%) –	–	1 (1%) –	2 (0.4%) –	–	8 (0.6%) –	2 (0.1%) –	10 (0.2%) –	12 (0.1%) *4 (0.0%)*	10 (0.1%) *1 (0.0%)*	0.273
Suspected TAA	3 (4%)	1 (3%)	4 (4%)	–	–	–	–	–	–	–	
AAA + TAA total ***ruptured***	3 (3%) *1 (1%)*	–	3 (2%) *1 (1%)*	–	–	–	–	–	2 (0.0%) –	1 (0.0%) –	
Unspecified AA	–	–	–	–	–	–	–	1 (0.0%)	10 (0.1%)	3 (0.0%)	
Dissection	1 (1%)	–	1 (1%)	2 (0.4%)	–	–	2 (0.1%)	2 (0.0%)	5 (0.0%)	18 (0.1%)	0.08
AA or dissection ***ruptured***	17 (18%) *3 (3%)*	1 (3%) –	18 (14%) *3 (2%)*	6 (1%) –	4 (1%) –	27 (2%) *2 (0.0%)*	16 (0.1%) *5 (0.0%)*	50 (1%) *8 (0.0%)*	64 (0.4%) *15 (0.1%)*	86 (0.7%) *13 (0.1%)*	<0.0005
Median age at AA diagnosis, y (25 and 75 percentiles)	–	–	63 (58-73)	50 (46-54)	76 (73-81)	–	–	65 (59-73)	66 (58-72)	70 (63-76)	0.61
Comorbid diseases in IA patients from 1995 to 2014	**n=69**	**n=20**	**n=89**	**n=405**	**n=251**	**n=1,142**	**n=1,580**	**n=2,722**	**n=15,652**	**n=10,391**	
ADPKD, n (%)	1 (1%)	1 (3%)	2 (2%)	0	0	19 (1%)	32 (1%)	51 (1%)	33 (0.2%)	7 (0.1%)	
Marfan, n (%)	0	0	0	0	0	0	0	0	3 (0.0%)	1 (0.0%)	0.663
Loeys-Dietz, n (%)	0	0	0	0	0	0	0	0	0	0	
Ehlers-Danlos, n (%)	0	0	0	0	0	0	0	0	0	0	
Hypertension, n (%)	63 (91%)	18 (90%)	81 (91%)	146 (45%)	245 (97%)	921 (81%)	1,123 (71%)	2,044 (75%)	8,780 (56%)	7,989 (77%)	0.001
Type 2 diabetes, n (%)	15 (22%)	5 (25%)	20 (22%)	34 (8%)	61 (24%)	174 (15%)	187 (12%)	361 (13%)	2,270 (14%)	1,742 (17%)	0.012
Atherosclerotic disease or hyperlipidamiea	23 (25%)	3 (9%)	37 (30%)	98 (24%)	172 (68%)	187 (16%)	158 (10%)	345 (13%)	5,764 (37%)	5,132 (49%)	<0.0005

Saccular IAs left + right	Fusiform IAs left + right
Mbif 2,013 33%	BA trunk 52 39%
ACoA 1,229 20%	ICA trunk 31 23%
BAbif 265 4%	VA trunk 15 11%
ICAbif 230 4%	M1 trunk 10 7%
Others 800 14%	Others 26 20%

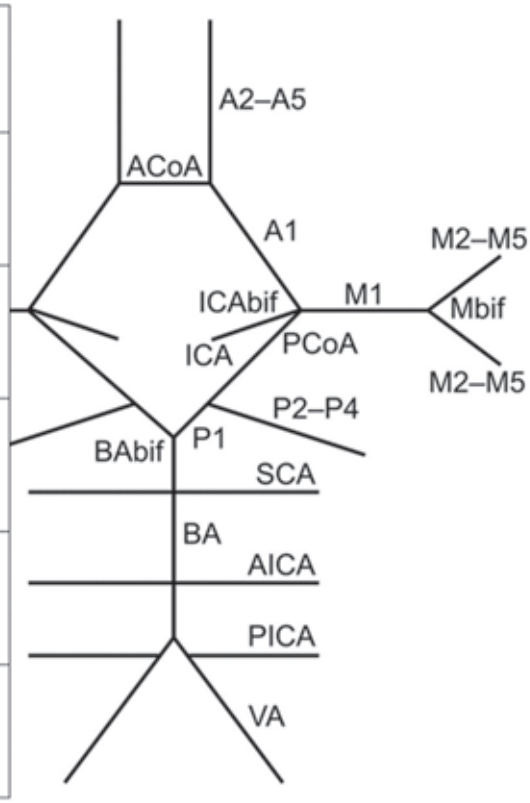

Figure 13 The most common locations of the 134 fusiform intracranial aneurysms (fIA) and the 6,097 saccular intracranial aneurysms (sIA) in descending order of frequency (the left side and the right side combined). The schematic illustration of the major intracranial arteries with the circle of Willis shows the major arterial bifurcations and segments (compare to Figure 1.).

Anterior circulation: ICA, the internal carotid artery up to the ICA bifurcation; ICAbif, ICA bifurcation; A1, the proximal segment of the anterior cerebral artery; ACoA, the anterior communicating artery; A2–A5, the distal segments of the anterior cerebral artery; M1, the proximal segment of the middle cerebral artery; Mbif, the bifurcation of the middle cerebral artery; M2–M5, the distal segments of the middle cerebral artery.

Posterior circulation: VA, the vertebral artery; PICA, the posterior inferior cerebellar artery; BA, the basilar artery; AICA, the anterior inferior cerebellar artery; SCA, the superior cerebellar artery; BAbif, the basilar tip bifurcation; P1, the proximal segment of the posterior cerebral artery; P2–P4, the distal segments of the posterior cerebral artery; PCoA, the posterior communicating artery.

6.3.2 Comparison of fIA patients and sIA patients

Aneurysmal subarachnoid haemorrhage (aSAH) had occurred in 26% of the 125 fIA patients and 69% of the 4,253 sIA patients ($p<0.0005$) (Table 10). Other clinically notable differences between the fIA and sIA patients were: age at diagnosis of IA (median 64 and 54 years, $p<0.0005$); male predominance (52% versus 45%, $p=0.11$); multiple fIAs versus multiple sIAs (6% versus 28%, $p<0.0005$); hypertension (91% versus 75%, $p=0.001$); and type 2 diabetes (22% versus 13%, $p=0.012$). However, ADPKD occurred equally often (2% versus 1%, $p=0.663$). None of the fIA patients with ADPKD had concurrent sIA. There were both fIA and sIA patients who

belonged to an sIA family (6% versus 14%, p=0.007). No patients with a diagnosis of Marfan syndrome, Loeys-Dietz syndrome or Ehlers-Danlos syndrome were identified in either patient group.

6.3.3 Comparison of fIAs and sIAs

In a comparison of the 134 fIAs and 6,097 sIAs, including the sIAs of the 22 fIA patients with both fIA and sIA, the largest sizes of the 102 unruptured fIAs were significantly larger than those of the 3,145 unruptured sIAs (17mm versus 4mm, p<0.0005). The 32 ruptured fIAs were significantly larger than the ruptured 2,952 sIAs as well (10mm versus 7mm, p=0.01). Among the unruptured IAs, the 102 fIAs preferred the arterial trunks of vertebrobasilar tree (VBA) (59%) and the trunk of the internal carotid artery (ICA) (23%) whereas the 3,145 sIAs were most frequent on the middle cerebral artery (MCA) bifurcation (45%) and the intracranial ICA (25%) (Figure 13, Table 11). Among the ruptured IAs, the 32 fIAs preferred the VBA trunks (50%) and the ICA trunk (25%) while the 2,925 sIAs were most frequent on the MCA bifurcation (33%) and the anterior communicating artery (ACoA) (31%) (Figure 13, Table 11).

In the 125 fIA patients, 29 fIAs (23%, median size 32 mm) caused symptoms of brain or cranial nerve compression in contrast to only 54 (1.3%, median size 28 mm) sIAs in the 4,253 sIA patients (Table 3). Of all 67 basilar trunk fIAs, 18 (27%, median size 38 mm) caused brainstem compression and three obstructive hydrocephalus. In the anterior circulation, two symptomatic fIAs were on the MCA and six on the ICA.

Table 11 Site and size distribution of the 134 fusiform and the 6,097 saccular intracranial aneurysms

Variables	134 fIAs			6,097 sIAs		
	Unruptured n (median size)	Ruptured n (median size)	Total n (median size)	Unruptured n (median size)	Ruptured n (median size)	Total n (median size)
Total	102 (17 mm)	32 (10 mm)	134 (15 mm)	3,145 (4 mm)	2,952 (7 mm)	6,097 (6 mm)
25 and 75 percentiles	*9-35 mm*	*6-19 mm*	*8-28 mm*	*3-7 mm*	*5-11 mm*	*4-9 mm*
A1	0	2 (15 mm)	2 (15 mm)	21 (3 mm)	14 (5 mm)	35 (3 mm)
ACoA	1 (15 mm)	1 (7 mm)	2 (11 mm)	390 (4 mm)	909 (7 mm)	1299 (6 mm)
A2 – A5	0	0	0	158 (3 mm)	153 (6 mm)	311 (4 mm)
ICA to ICAbif	23 (10 mm)	8 (9 mm)	31 (10 mm)	790 (4 mm)	626 (7 mm)	1416 (6 mm)
M1 to Mbif	9 (9 mm)	1 (30 mm)	10 (9 mm)	1,424 (4 mm)	963 (9 mm)	2387 (6 mm)
M2 – M5	4 (7 mm)	3 (23 mm)	7 (8 mm)	113 (3 mm)	25 (6 mm)	138 (3 mm)
PCoA	0	0	0	3 (11 mm)	2 (8 mm)	5 (8 mm)
P1	1 (9 mm)	0	1 (9 mm)	14 (3 mm)	11 (6 mm)	25 (3 mm)
P2 – P4	4 (8 mm)	1 (7 mm)	5 (8 mm)	2 (13 mm)	8 (5 mm)	10 (5 mm)

BA	46 (25 mm)	6 (8 mm)	52 (25 mm)	131 (7 mm)	134 (9 mm)	265 (8 mm)
SCA	1 (8 mm)	0	1 (8 mm)	54 (3 mm)	25 (7 mm)	79 (4 mm)
AICA	0	0	0	0	1 (8 mm)	1 (8 mm)
PICA	6 (10 mm)	2 (9 mm)	8 (10 mm)	33 (4 mm)	67 (5 mm)	100 (5 mm)
VA	7 (28 mm)	8 (10 mm)	15 (19 mm)	9 (12 mm)	10 (9 mm)	19 (10 mm)
Others	0	0	0	3 (2 mm)	4 (8 mm)	7 (3 mm)

* Median of largest sIA diameter or median of largest fIA length or diameter.
A1, the proximal segment of the anterior cerebral artery; ACoA, the anterior communicating artery; A2–A5, the distal segments of the anterior cerebral artery; ICA, the internal carotid artery; ICAbif, the ICA bifurcation; M1, the proximal segment of the middle cerebral artery; Mbif, the bifurcation of the middle cerebral artery; M2–M5, the distal segments of the middle cerebral artery; PCoA, the posterior communicating artery; P1, the proximal segment of the posterior cerebral artery; P2–P4, the distal segments of the posterior cerebral artery; BA, the basilar artery; SCA, the superior cerebellar artery; AICA, the anterior inferior cerebellar artery; PICA, the posterior inferior cerebellar artery; VA, the vertebral artery; others, not classified.

6.3.4 AA in 4,253 sIA patients

There were 48 (1.1%) sIA patients with a diagnosed AA (37 AAA, 10 TAA, 1 undefined AA) and two patients with diagnosed aortic dissection (Figure 10, Table 10). Of the 48 AAs, eight (17%) had ruptured. Of the 48 patients, 37 (79%) were males, 46 (96%) had diagnosed hypertension and 22 (48%) had diagnosed atherosclerotic disease. The median ages at the diagnosis of sIA and AA were 57 years and 66 years ($p=0.006$); in nine patients, the AA diagnosis preceded the sIA diagnosis (Figure 14, panel B). The 4,253 sIA patients had significantly more often AA than their 17,825 first-degree relatives (1.1% versus 0.3% $p<0.0005$) and their 12,669 matched population controls (1.1% versus 0.5%, $p<0.0005$). Diagnosed or suspected AAs were significantly more prevalent in the 125 fIA patients than in the 4,253 sIA patients (14% versus 1.1%, $p<0.0005$).

6.3.5 AA in 125 fIA patients

There were 17 (14%) fIA patients with a diagnosed AA (4 TAA, 12 AAA) or suspected AA (4 widened thoracic aortas in chest radiographs [two patients] or thoracic echocardiographs [two patients] indicative of TAAs) and one patient with an aortic dissection (Figure 10, Table 10). Of the 17 AAs, three (17%) had ruptured. Of the 17 patients, 12 (71%) were males, 16 (94%) had diagnosed hypertension and nine (53%) had diagnosed atherosclerotic disease. The median ages at the diagnosis of fIA and AA were 64 and 63 years (Figure 14, panel A); in eight patients, the AA diagnosis preceded the fIA diagnosis. The 125 fIA patients had significantly more often AA than their 450 first-degree relatives (14% versus 0.9%, $p<0.0005$) and their 340 matched population controls (14% versus 1.2%, $p<0.0005$) (Table 10).

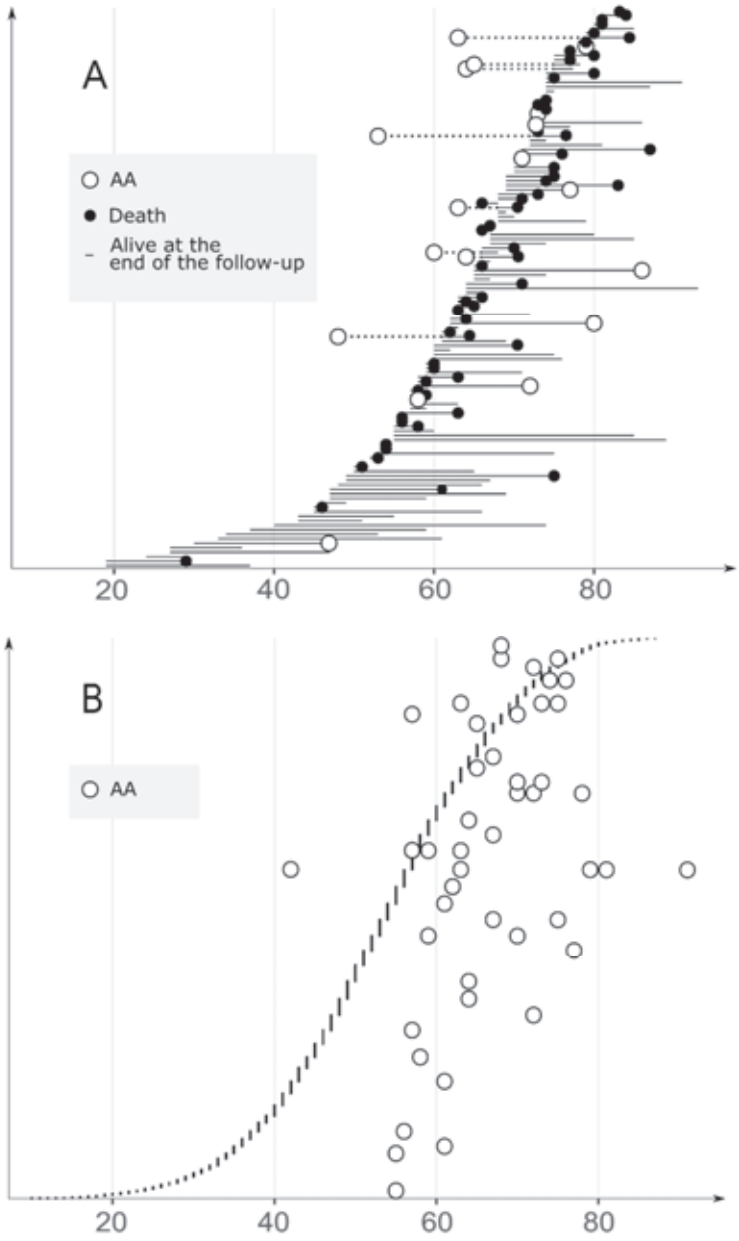

Figure 14 (A) Distribution of the ages, in ascending order, of the 125 fusiform intracranial aneurysm (fIA) patients (32 ruptured, 93 unruptured) at the diagnosis of the fIA. The ages at the diagnosis their 17 aortic aneurysms (AA) are shown (white circles). The lifelines of the fIA patients from either diagnosis (fIA or AA) until the AA diagnosis, death (without AA diagnosis, black circles) or the last follow-up (without AA diagnosis, end of lifeline) are shown.

(B) Distribution of the ages, in ascending order, of the 4,253 saccular intracranial aneurysms (sIA) patients (2,923 ruptured, 1,330 unruptured) at the diagnosis of their sIA. The ages at the diagnosis of their 48 aortic aneurysms (AA) are shown (white circles). The lifelines of the sIA patients with diagnosed AA are omitted for the sake of clarity. The median ages at the sIA diagnosis (dashed vertical line) and AA diagnosis (continuous vertical line) are shown.

6.3.6 Multivariate analysis of independent risk factors for AA in fIA and sIA patients

In the multivariable regression analysis, fusiform IA morphology (SHR 7.6, 95% CI 3.9–14.9, p<0.0005), diagnosed atherosclerotic disease or use of lipid-lowering medication (SHR 4.4, 95% CI 2.3–8.2, p< 0.0005), and male gender (SHR 3.1, 95% CI 1.5–6.4, p=0.002) were independent risk factors for AA. However, hypertension (SHR 6.4, 95% CI 0.9–47.2, p=0.07), type 2 diabetes (SHR 1.4, 95% CI 0.7–2.7, p=0.36) and history of IA rupture (SHR 0.4, 95% CI 0.2–1.8, p=0.26) were not.

6.3.7 Sequencing of fIA patients

Of the 41 fIA patients alive, 33 were sequenced using an AA gene panel of 37 genes. Six fIA patients each carried a different rare variant (MAF <0.01): splice-donor variant *COL5A2* c.322+1G>C (NM_000393.3), four missense variants each in one patient: *SKI* c.1582G>C, p.(Ala528Pro) (NM_003036.3); *FBN1* c.3571G>A, p.(Asp1191Asn) (NM_000138.4); *MYH11* c.4903T>A, p.Ser1635Thr) (NM_022844.2); *COL11A1* c.278G>T, p.Gly93Val) (NM_080629.2) and a synonymous variant *COL3A1* c.1038C>T, p.(Ser346=) (NM_000090.3) (Table 12). The splice-donor variant in *COL5A2* was classified as likely pathogenic. There are 21 individuals heterozygous for the *COL5A2* c.322+1G>C variant in the Genome Aggregation Database (gnomAD, n>120,000 exomes and >15,000 genomes). This variant affects consensus splice site, and all five components of Alamut splicing software (SSF, MaxEnt, NNSPLICE, GeneSplicer, HSF) predict that this variant breaks the wild type donor site but does not generate a near-by in-frame cryptic splice site. It has been detected in clinical testing in one affected individual by GeneDx (ClinVar 213136), and two additional affected patients with either ascending aortic dissection or multiple aneurysms including IA have been identified by Blueprint Genetics (Juha Koskenvuo, MD PhD, unpublished data, 2019). One of the tested healthy family members did not carry the variant, which further supports pathogenicity of the variant. However, variant's allele frequency is relatively high, at least suggesting that it may not be fully penetrant. *MYH11*, *COL11A1*, and *FBN1* variants were classified as of uncertain significance whereas *SKI* and *COL3A1* were deemed to be likely benign.

6.3.8 Literature review

We identified 27 published family trees with co-occurrence of IAs and AAs (Table 8). In 21 family trees the morphology of the IAs, whether fusiform or saccular, was not reported. There were nine IA patients with AA and 57 IA patients with no AA. There were 95 AA (58 TAA, 7 AAA, 30 unspecified AA) patients without IA.

Table 12 Rare variants found among 33 patients with fusiform intracranial aneurysm in the genetic screening of 37 genes associated with aortic aneurysms

Gene	Effect on genomic DNA	Effect on protein transcript	Allele frequency in gnomAD	Predicted effect on protein function	Clinical significance
SKI	c.1582G>C	p.(Ala528Pro)	7.68e-05	Missense variant	Likely benign
FBN1	c.3571G>A	p.(Asp1191Asn)	1.08e-05	Missense variant	VUS
COL3A1	c.1038C>T	p.(Ser346=)	3.97e-05	Synonymous variant	Likely benign
MYH11	c.4903T>A	p.(Ser1635Thr)	0	Missense variant	VUS
COL11A1	c.278G>T	p.(Gly93Val)	0	Missense variant	VUS
COL5A2	c.322+1G>C	N/A	7.58e-05	Splice donor variant	Likely pathogenic

6.4 DISCUSSION

6.4.1 Comparative characteristics of fIA and sIA diseases

To our knowledge, this is the first population-based study comparing the characteristics of the fIA disease (125 patients with 134 fIAs) and the sIA disease (4,253 with 6,097 sIAs). Fusiform IAs are rare, comprising 2.2% of all IAs in our study, and sizeable published series are few.[165] Like aortic aneurysms, fIAs are dilatations of arterial segments, while sIAs are saccular pouches usually formed at the artery forks (Figure 9). The site distribution of the sIAs and the fIAs differs significantly[144,318]: in our study, 56.7% of the fIAs but only 7.6% of the sIAs were located on the vertebrobasilar artery complex (Figure 13, Table 10).

The fIA patients were significantly older than the sIA patients, less likely to present with IA rupture, and more likely diagnosed with hypertension, type 2 diabetes, hyperlipidaemia or atherosclerotic disease (Table 10). In the fIA patients of this cohort, hypertension and type 2 diabetes were even more frequent (91% and 22%) than in the previously reported fIA cohorts.[34,319,320] ADPKD, an unusual monogenic risk factor for the sIA disease[10], previously reported to occur in some 2% of patients with vertebrobasilar fIAs[34], occurred equally in the fIA and the sIA patients (Table 10). Multiple fIAs on arterial trunks were less frequent than multiple sIAs on bifurcations (6% versus 28%) (Table 10). In previous cohorts of patients with vertebrobasilar dolichoectasia, the reported frequency of diffuse dolichoectatic lesions has varied considerably with a range of 16–45%.[40,319] Different morphologies make size comparison of the fIAs and sIAs impractical; however, unruptured and ruptured fIAs were larger than unruptured and ruptured sIAs, and the pronounced size difference underlines and explains the different rates of aneurysm symptomaticity (Table 11). Due to their larger size and preference for the posterior fossa, the fIAs often caused symptoms by compression: brainstem compression, cranial nerve symptoms and obstructive hydrocephalus.

Few studies on the histopathology and molecular biology of the fIA wall, resected during surgery or at autopsy, are available. In one study, walls of eight fIAs displayed fragmentation of internal elastic lamina, neoangiogenesis within thickened intima, intramural haemorrhage and thrombus formation.[186] Similar changes are observed not only in sIAs but also in AAAs and TAAs.[189,190,321] Fusiform IAs have been linked to atherosclerotic risk factors, but the association of atherosclerosis with fIAs or its role as causal factor is complex and unclear.[8]

The distinctions between and the terminology regarding the spectrum of conditions that manifest as different forms of non-saccular dilatations of intracranial arteries are often unclear. Dolichoectasia, elongation and dilatation of intracranial arteries (Figure 9), is most common in the vertebrobasilar complex.[8] In neuroimaging (CT, CT angiography [CTA], MRI, MR angiography [MRA], digital subtraction angiography [DSA]), dolichoectasia can be difficult to distinguish from fusiform IAs, and the two may represent the same disease spectrum and pathogenesis.[8] Acute dissection is considerably less frequent in the intracranial arteries than in the cervical

arteries, and is a rare cause of subarachnoid haemorrhage or brain infarction.[322] There are data indicating that intracranial dissection may develop into a chronic fusiform aneurysm.[187]

6.4.2 AA in fIA and sIA patients

To our knowledge, this is also the first population-based study to investigate the occurrence of aortic aneurysms in both fIA and sIA patients (Figures 10 and 14), and in the first-degree relatives and the matched population controls for the both patient groups (Figure 10, Table 10). The 125 fIA patients had significantly more often AA than their 450 first-degree relatives (14% versus 0.9%) and their 340 matched population controls (14% versus 1.2%). In a recent retrospective study of 139 patients with fIA or dolichoectasia, similar proportion of the patients (12% and 14%) had concomitant AAA (Table 8), equal to 14% in this study. In other studies, fIAs may have been excluded or not distinguished from sIAs (Table 8).[40] The risk of AA seems to warrant the screening of aortas of all fIA patients with MRA or CTA.

The 4,253 sIA patients had clearly fewer diagnosed AAs during the follow-up than the fIA patients (1.1% versus 14%) (Figures 10 and 14), but, nevertheless, more than their 17,825 first-degree relatives (1.1% versus 0.3%) and their 12,669 matched population controls (1.1% versus 0.5%) (Figure 10, Table 10). The 48 sIA patients with AA were, on average, males, diagnosed with hypertension, with a substantial portion carrying atherosclerotic diseases. Despite the older age and higher burden of comorbid diseases in the fIA patients, as compared to the sIA patients, the fusiform IA morphology was the most important risk factor for AA in a multivariate model alongside the recognised risk factors, indicating that the increased AA risk in the fIA patients is not contributable to the traditional risk factors alone. No robust data on smoking was available for the multivariate model. The identified risk factors for AA in IA patients and the equivocal or protective role of diabetes against AA are well in line with previous research.[321]

6.4.3 Genetics of fIA disease in relation to AA disease

We hypothesised that the rare fIAs share, in addition to their fusiform shape, genomic and acquired risk factors with AAs. In our review of the literature, we identified 27 families containing both IA patients and AA patients (Table 9). Among the 523 members of these families, 57 IA patients and 95 AA (58 TAA, 7 AAA, 30 unspecified AA) patients but only 9 patients with both IA and AA were identified. In most cases, the morphology of the IAs, whether fusiform or saccular, was not reported. A previous meta-analysis of genome-wide association studies (GWAS) of IA, TAA and AAA cohorts did not find evidence for shared genetic risk of IAs, TAAs and AAAs; however, in that study, fIA patients were not distinguished from the sIA patients.[281] The genetics of the sIA disease remain elusive.[9]

In the present study, none of the 125 fIA patients had been diagnosed with inherited traits predisposing to AAs, including Marfan, Loeys-Dietz or Ehlers-

Danlos syndromes. We were unable to identify any fIA families, but six per cent of the fIA patients belonged to an sIA family. Interestingly, concomitant fIA and sIA were seen in 18% of the fIA patients, suggesting susceptibility of these patients to aneurysms in general. Considerable co-occurrence of fIAs and sIAs has been reported previously in some studies.[40] We sequenced 33 fIA patients with a panel of 37 genes associated to AA, and found only one likely pathogenic variant (*COL5A2* c.322+1G>C), which would likely predispose to classic Ehlers-Danlos syndrome or TAA or thoracic aortic dissection.

The molecular pathologies of TAA and AAA are divergent.[323] A substantial proportion of TAAs occur in association with a defined genetic syndrome or an identifiable single-gene mutation. A focused or genome-wide testing of the proband and, in the case of a positive finding, the first-degree relatives, is recommended in patients presenting with syndromic features, positive family history or absence of traditional cardiovascular risk factors. Even though hereditary risk to AAA is well-established, known causative single-gene mutations are few.[324] Consequently, family history affects the decision threshold of screening for the first degree relatives of AAA patients.[32] However, genetic counselling is recommended if the AAA disease cannot be solely explained by a non-genetic cause.[33]

6.4.4 Our strengths

Our study has several strengths. The publicly-funded Finnish health care system is universal, which reduces bias to minimum in population-based disease databases. Neurosurgery of the Kuopio University Hospital (KUH) is the sole provider of acute and elective neurosurgical services for Eastern Finland, including unruptured and aneurysmal SAH patients. The Kuopio IA Patient and Family Database has incorporated clinical data for both the IA patients and their relatives and matched population controls from the national registries, using the Finnish personal identity codes. The data quality of the Finnish national health registers has been shown to be good.[325]

6.4.5 Our limitations

However, the study has some limitations. Aortic aneurysms have not been screened in Finland either on a population level, in patients with intracranial aneurysms or in patients with stroke. Unruptured IAs, with an estimated lifetime prevalence of 2%–3%, and AAs, with an estimated lifetime prevalence of 1%–8%, are increasingly diagnosed as incidental findings in the imaging of the head or the body for other reasons in the elderly population. As both sIA and fIA patients may have had shortened survival, their controls may have accrued longer follow-up with age-related increasing prevalence of AA, possibly leading to some attenuation in our finding of increased AA prevalence in IA patients. Our data contained 68 AAs in IA patients but only 67 could be accurately verified. Consequently, our available data did not allow exact anatomical classification of all the AAs. Furthermore, the

specificity of chest radiograph for TAA, used in two fIA patients as the basis diagnosis, is not high enough for definite diagnosis of TAA. The determination of the disease status of the comorbid diseases was in many cases based on medication use without knowledge of the indication of the prescription. Among the 125 fIA patients, only a small subgroup was available for the genotyping. The genotyping included only genes the mutations of which are known to associate with AA.

6.4.6 Suggested further research

Fusiform IAs that involve perforators, branches and bifurcations of the cerebral arteries are difficult to treat with the present microsurgical, endovascular and bypass techniques.[192] Since fIAs and AAs share the fusiform shape and, possibly, pathogenetic mechanisms, and as fIAs and AAs partially co-occur, cellular and molecular biology data from AA walls may help to develop pharmacological treatment that would stabilise the fIA wall and reduce its growth. In sIA patients, the risk of AA diagnosis was low in our study, and may not justify screening for AA of sIA patients, but it remains an underestimate in the absence of prospective screening studies of sIA patients for incidental AA.

6.5 CONCLUSIONS

In our study, without any screening for AA, approximately 1% of the sIA patients had diagnosis for AA, in contrast to 0.3% of their first-degree relatives and 0.5% of their matched population controls. These data suggest that screening for AA in sIA patients is not generally indicated. In fIA patients the risk of AA was 14%. This warrants screening of aortas of all fIA patients with MR angiography or CT angiography. The AA gene panel with 37 previously known AA-associated genes in 33 fIA patients identified likely disease-causing variant only in 1/33 (3%) of the patients. This observation suggests that fIA and AA may share genetic background in some cases but larger cohorts are needed to validate or dispute this association.

7 DISCUSSION

7.1 NEUROFIBROMATOSIS TYPE 1 AND INTRACRANIAL ANEURYSM DISEASE

The association of NF1 and intracranial aneurysms was first proposed in the 1960s based on a small patient series.[326] Since then, the published results on the alleged relationship have been conflicting. Systematic MRI screenings of NF1 have been studied only in the setting of screenings for optic pathway gliomas in children.[327]

The hazard of SAH was not increased among the patients of the Finnish NF1 database. Subarachnoid haemorrhage is a medical emergency that almost never remains undiagnosed. Consequently, based on the results of this study, a clinically significant excess risk of SAH can be ruled out with reasonable certainty. Our cohorts did not allow for an analysis on the propensity of IA rupture in the NF1 patients, nor their risk of rupture in the follow-up.

An increased overall risk of stroke in NF1 patients has been observed in a sizeable retrospective study. It is notable that the results of this study were driven by the grossly increased risk of intracerebral haemorrhage, whereas the incidence of ischaemic stroke and aSAH were not increased in comparison to the control population.[30] Although the incidence of aSAH was not the primary investigated variable, these results are well in line with our study. The number of case reports and patient series reporting different cerebrovascular and other vascular abnormalities in association with NF1 is considerable (Table 5), and the increased risk of intracerebral haemorrhage could allude to such an association as well. However, if a lack of aneurysmal origin is assumed, efforts to reduce this risk by angiographic screening to identify targets for preventive operative treatment would be rendered moot.

Despite the predominance of neurocutaneous manifestations in the clinical picture of NF1, vascular complications and aneurysmal dilatations among them have been reported to occur as a consequence of NF1 in the vasculature. The *NF1* gene is expressed in numerous tissues, and there are animal models indicating a mechanistic link between its function and the development of vascular complications.[216,217,328] Although there are no prospective data on the association of NF1 with arterial aneurysms in the intracranial nor the systemic vasculature, the accumulated evidence is more robust for the latter.[27] The embryological origin and the normal histologic structure of intracranial and extracranial arteries are partially different; it would not be unreasonable to assume that a mutation affecting the structural stability of some blood vessels of the body might not have a similar effect elsewhere.

The life expectancy of NF1 patients is 8–15 years shorter than that of the general population; for NF1 patients in Finland, the mean age at death is 52 years.[201,329] An association with and a predisposition to several types of neoplasia are central causes

for decreased survival. However, an increased risk of cerebrovascular disease has been suggested to be a contributing factor.[30] Given the age-dependent incidence of both incidental sIA disease and aSAH, the decreased life expectancy associated with NF1 presents the present study with a natural limitation. Although the patients and controls were matched for statistical analysis, the relative rarity of the aSAH in both the NF1 patients and the controls is an impediment to the generalisability of the results.

Despite the limitations of the study, which are intrinsic to the nature of the data – including the inability to correct for known SAH risk factors, the nature of the studied disease entities and the provisions that must be made in regard to the potential association of NF1 and cerebrovascular incidents as a group – an association between aneurysmal SAH and NF1 can be refuted relatively reliably based on the present study. Aneurysmal SAH is a medical and neurosurgical emergency rarely left undiagnosed, and the Finnish national NF1 database is extensive, ascertained and combined with extensive matched population data. Consequently, a register-based approach is well-suited for a study of their association.

7.2 SACCULAR INTRACRANIAL ANEURYSMS IN OFFSPRING WHEN PARENTS ARE CONCORDANT FOR SACCULAR INTRACRANIAL ANEURYSM DISEASE

The results from traditional linkage studies, genome-wide association studies and exome-wide association studies on the heritability of the sIA disease have not reinforced each other. Putative results from the present family study further assert the heterogenic nature of the sIA disease: the clinical picture of the disease ranges from extremely penetrant to considerably more indolent, even in families where the genetic predisposition, broadly classified as familial sIA disease, is identical.

The small sample size and incomplete radiologic screening of many of the families are considerable limitations to this study. Furthermore, the characterisation of the families was lacking, particularly in regard to smoking. However, it appears that the offspring of individuals with sporadic sIA disease, even when both parents are carriers, are not at a grossly increased risk for sIA disease. Although silent disease in the offspring of these families could not be definitively excluded based on the available data, it is noteworthy that aggressive disease manifesting as aSAH at a young age would have been evident. Exceptionally aggressive disease observed in some of the families with familial background, in turn, underlines the importance of individual assessment when planning the frequency and starting age of screening for sIA disease. An evident hypothetical explanation for this observation would be rare sIA risk variants with a large effect-size segregating in these families. No families in which both parents were concordant for familial sIA disease were found. However, in light of the silent nature of sIA disease, it is possible that such families have been misclassified.

In previous observational studies on sIA families, the risk of sIA disease has been somewhat higher in siblings of the index patient than in their children, even after correcting for age.[97] Reasons for this observation are unclear. Parents of the index patients are often disproportionately unavailable or unfit for screening.

The risk of many complex diseases is additively increased when both parents, as opposed to only one, are affected by the same disease (Table 6). A clearly speculative explanation could assume that if both parents of the family were to harbour an above-average genetic predisposition to sIA disease or were asymptomatic carriers, the risk of overt sIA disease in their offspring would be increased in comparison to the children of their children, in whom the genetic risk would once more be more diluted. Such a phenomenon is not supported by the results of our study. Instead, the effect of different secular trends on the risk of sIA formation and rupture, for example, a decrease in smoking,[52] could at least partially explain the decreased risk of sIA disease in the younger birth cohorts and possibly relate to the results of our study.

Exome-wide analysis has been employed in the study of sIA disease.[129-136] Sequencing the whole exome or genome brings about significant problems in the analysis of the results. In contrast to GWA studies, the aim of the targeted exome, whole exome or whole genome sequencing is to also identify possible rare variants associated with the investigated trait. The low frequency of the tested variants and the considerably larger number of genetic variants tested for an association lead to considerable trouble with the required sample size and statistical inference when the study is performed on a population level.[330] For example, a cohort of 10 000 cases and controls would be grossly underpowered to detect a variant with a minor allele frequency of 0.5% and an effect size (OR) of 2.[330] The two approaches to solving this conundrum, family-based analysis and utilisation of population isolates, which in some sense is an extension of the former,[330] have both been utilised in the study of sIA disease.[129-136]

Rare variants that lead to change or loss of gene or protein function are relatively common in seemingly healthy individuals: analyses based on the 1000 Genomes Project estimate that a typical individual harbours more than ten potentially severe disease alleles and hundreds of potentially disadvantageous variants.[331] Even known disease-causing mutations were encountered in both the heterozygous and homozygous state. Accordingly, reduced penetrance, defined as a situation in which a genetic variant causes a given phenotype in some individuals but not in all carriers, is not an uncommon phenomenon. Small effect-size, a characteristic of most risk variants identified in the GWA studies, is a conceptually different phenomenon related to the heredity of complex diseases. Reduced penetrance can be explained by both interaction with environmental factors, epigenetic modifications and different genetic factors related to the risk variant itself or its interaction with other loci.[331] The complexity of the functional interplay of risk variants with incomplete penetrance with their genetic and environmental backgrounds pose challenges to the classical family-based linkage analysis.[330]

Despite these challenges, exome-wide analysis appears to be the most natural and efficient methodology for analysis of family data on a molecular genetic level in the research of sIA disease. Descriptive studies remain powerful in generating hypotheses and providing information for clinical decision-making.

In clinical practice, it is important to construct the maternal and paternal family trees of all patients presenting with an unruptured sIA or aSAH, as identifying an sIA family has clear clinical implications. Both European and American guidelines recommend screening for IAs in families with more than one person affected with IA.[141,275]

7.3 AORTIC ANEURYSMS IN PATIENTS WITH INTRACRANIAL ANEURYSMS

Evidence for an association between intracranial aneurysms and aortic pathologies has accumulated over the past three decades. The relationship of aortic and intracranial aneurysms has not been investigated as thoroughly as that of, for example, coarctation of the aorta,[4,276,277] and the results of the previous studies are partially conflicting.[34-41,332,333] The treatment of abdominal aortic aneurysms in particular has evolved rapidly, and as the endovascular treatment of AAA has become more common, a greater proportion of patients has become potentially eligible for preventive operative treatment.[220]

An excess of both thoracic and abdominal aortic aneurysms was observed in the IA patients of our study. The previously reported associations between bicuspid aortic valve and aortic coarctation, two vascular conditions with a significant familial component,[1,2] and intracranial aneurysms have been hypothesised to relate to the shared embryological origin of both the left ventricular outflow tract, the aortic arch and its branches, and the arteries of the neck and head.[3-5] The smooth muscle cells of the abdominal aorta are derived from the splanchnic mesoderm.[334] Interestingly, it appears that smooth muscle cells of the arteries of the posterior cerebral circulation are embryologically of mesodermal origin as well.[5] The smooth muscle cells of different origins respond differently to certain cytokine and growth factor stimuli *in vitro*.[335] The different location distribution of intracranial aneurysms occurring together with aortic aneurysms reported in one patient cohort is likewise intriguing.[38] The majority of the anterior circulation IAs that co-occurred more often with aneurysms of the ascending thoracic aorta were located on the middle cerebral artery in the anatomical classification used. The number of posterior circulation IAs was considerably lower, with no statistically significant differences in the location distribution.

It could be hypothesised that the high prevalence of AAA observed in the previous patient series of vertebrobasilar fusiform IA and dolichoectasia could be related, in addition to the aggregation of acquired cardiovascular risk factors, to some underlying defect affecting a particular cell lineage. It should be noted that fusiform IA morphology was the most important risk factor for AA in IA patients in a

multivariate model alongside the recognised risk factors, implying that the increased risk of AA in the fIA patients cannot be explained by traditional cardiovascular risk factors alone. However, in our study, the risk of AAA was increased in both the fIA patients, in whom the posterior cerebral circulation is usually affected, and the sIA patients, in whom the majority of intracranial aneurysms are located on arterial bifurcations of the anterior circulation. Furthermore, the prevalence of TAA was increased in the fIA patients in comparison to the sIA patients and the population controls.

It is difficult to ascertain a causal link between aortic and intracranial aneurysms. Traditional cardiovascular risk factors are contributing factors in both intracranial and aortic aneurysms. Smoking, hypertension and increasing age are strong risk factors for both thoracic and abdominal aortic and intracranial aneurysms.

The relationship of atherosclerosis and fusiform IAs is of particular interest. The calcification of fIAs and dolichoectatic aneurysms is common, and atherosclerosis has been traditionally linked to their formation.[318,336,337] However, several patient series have not demonstrated an association between extracranial atherosclerotic arterial disease and nonsaccular intracranial aneurysms. In line with these findings, the fIA patients of this study were less likely than their population controls to be diagnosed with an atherosclerotic disease or to be treated for dyslipidaemia.

Based on the present study, the co-prevalence rate of fusiform IAs and AAs seems to be clinically significant. However, the incomplete coverage of imaging among the IA patients, their relatives and their controls, in addition to characteristics of the national hospital discharge register that does not encompass all health care contacts, may have introduced bias into the data. To be justified, the overall benefits of a screening programme should exceed the harm caused by overdiagnosis and overtreatment.[338,339] On the other hand, case-finding and subsequent treatment should be cost-effective.[338,339] It is not possible to assess whether fIA-AA screening would meet these conditions based on our data. Based on a hypothetical model of co-prevalence of 7.7% of AAAs and IAs, it has been estimated that systematic screening for AAAs in patients with IAs would be cost-effective.[340] The true prevalence of AA disease in sIA patients is not estimable based on this study. However, it appears that the total prevalence of diagnosed AAs, particularly ruptured AAs, is not high enough to merit a systematic screening of all sIA patients for aortic vascular pathology.

The main impediment for AA screening for AAs in fIA patients is probably the relatively poor prognosis associated with the fIA disease. The annual mortality rate of vertebrobasilar fIAs is high, 13% in one estimate.[165] In the present study, overall mortality was high and the prognosis after the fIA diagnosis poor. The course of the fIA disease was highly variable, however, with some patients accruing decades of follow-up after the first diagnosis of an fIA. In clinical practice, the overall situation should be considered when suggesting screening for an fIA patient for aortic aneurysms. Rupture of the AA was not the symptom leading to the diagnosis in the majority of cases. AA rupture occurred in 4% of all fIA patients.

There is no medical therapy with shown efficacy for prevention of AAA growth and rupture. Research on the topic, however, is active. Given the morphological, haemodynamic and histological similarities between fIA (particularly vertebrobasilar fIA) and AAA, the research on AAA offers a window for future research and possible treatment modalities in the difficult-to-treat fIA disease.

8 CONCLUSIONS

In conclusion:

I) The risk of aSAH is not increased in patients with NF1. The number of NF1 patients among a population-based database of IA patients was well within the population prevalence. No evidence for an association between NF1 and neither saccular nor fusiform intracranial aneurysms was found.

II) Biparental sporadic-sporadic exposure does not seem to increase the risk of a diagnosed sIA disease in the offspring. The risk of sIA diagnosis is substantially increased when both parents are diagnosed with sIA disease and at least one parent belongs to an sIA family.

III) The prevalence of aortic aneurysms is slightly increased in sIA patients but significantly increased in fIA patients compared to their matched population controls and first-degree relatives. In fIA patients, the risk of AA was 14%. This supports the screening of fIA patients' aortas with MR angiography or CT angiography, depending on the overall clinical situation of the fIA patient. Fusiform intracranial aneurysms and AA may share a genetic background, but larger cohorts are needed to confirm or refute this association.

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ORIGINAL PUBLICATIONS (I – III)

APPENDICES

Appendix 1. The genes included in the Aorta Panel.[341] AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; XL, X-linked, XLD; X-linked dominant, XLR; X-linked recessive. ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in the ClinVar database.[342] HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database.[343]

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCC6	Pseudoxanthoma elasticum	AR	352	377
ABL1	Congenital heart defects and skeletal malformations syndrome (CHDSKM)	AD	30	5
ACTA2	Aortic aneurysm, familial thoracic, moyamoya disease, multisystemic smooth muscle dysfunction syndrome	AD	20	76
ADAMTS10	Weill-Marchesani syndrome	AR	8	14
ADAMTS17	Weill-Marchesani-like syndrome	AR	6	7

ADAMTS2	Ehlers-Danlos syndrome	AR	8	11
ADAMTSL4	Ectopia lentis, isolated	AR	11	27
ALDH18A1	Spastic paraplegia, Cutis laxa	AD/AR	22	30
ATP7A	Menkes disease, occipital horn syndrome, spinal muscular atrophy, distal, X-linked 3	XL	116	354
B3GAT3	Multiple joint dislocations, short stature, craniofacial dysmorphism, congenital heart defects	AR	6	13
BGN	Spondyloepimetaphyseal dysplasia, X-linked, Meester-Loeys syndrome	XL	8	7
CBS	Homocystinuria due to cystathionine beta-synthase deficiency	AR	88	205
COL1A1	Ehlers-Danlos syndrome, Caffey disease, osteogenesis imperfecta type 1, osteogenesis imperfecta type 2, osteogenesis imperfecta type 3, osteogenesis imperfecta type 4	AD	352	962
COL1A2	Ehlers-Danlos syndrome cardiac valvular form, Osteogenesis imperfecta type 1, Osteogenesis imperfecta type 2, Osteogenesis imperfecta type 3, Osteogenesis imperfecta type 4	AD/AR	186	509
COL2A1	Avascular necrosis of femoral head, rhegmatogenous retinal detachment, epiphyseal dysplasia, with myopia and deafness, Czech dysplasia, achondrogenesis type 2, platyspondylic dysplasia Torrance type, hypochondrogenesis, spondyloepiphyseal dysplasia congenital (SEDC), spondyloepimetaphyseal dysplasia (SEMD) Strudwick type, Kniest dysplasia, spondyloperipheral dysplasia, Mild SED with premature onset arthrosis, SED with metatarsal shortening, Stickler syndrome type 1	AD	180	561
COL3A1	Ehlers-Danlos syndrome	AD	520	631
COL4A5	Alport syndrome	XL	704	992

COL5A1	Ehlers-Danlos syndrome	AD	101	154
COL5A2	Ehlers-Danlos syndrome	AD	24	35
EFEMP2	Cutis laxa	AR	14	16
ELN	Cutis laxa, supravalvular aortic stenosis	AD	78	113
ENPP1	Arterial calcification, hypophosphatemic rickets	AR	22	72
FBLN5	Cutis laxa, macular degeneration, age-related	AD/AR	13	22
FBN1	MASS syndrome, Marfan syndrome, acromicric dysplasia, geleophysic dysplasia	AD	1465	2679
FBN2	Congenital contractural arachnodactyly (Beals syndrome)	AD	50	97
FKBP14	Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy, and hearing loss	AR	5	6
FLNA	Frontometaphyseal dysplasia, osteodysplasty Melnick-Needles, otopalatodigital syndrome type 1, otopalatodigital syndrome type 2, terminal osseous dysplasia with pigmentary defects	XL	133	257
FOXE3	Aphakia, congenital primary, anterior segment mesenchymal dysgenesis, cataract 34, aortic aneurysm, familial thoracic	AR/AD	9	29
GATA5	Familial atrial fibrillation, Tetralogy of Fallot, single ventricular septal defect	AD	5	32
HCN4	Sick sinus syndrome, Brugada syndrome, left ventricular non-compaction cardiomyopathy (LVNC)	AD	8	34
LOX	Aortic aneurysm, familial thoracic 10	AD	6	7

MAT2A	Complement system	AD/AR		2
MED12	Ohdo syndrome, mental retardation, with Marfanoid habitus, FG syndrome, Opitz-Kaveggia syndrome, Lujan-Fryns syndrome	XL	29	30
MFAP5	Aortic aneurysm, familial thoracic	AD	2	3
MYH11	Aortic aneurysm, familial thoracic	AD	16	48
MYLK	Aortic aneurysm, familial thoracic 7	AD	16	28
NOTCH1	Aortic valve disease, Adams-Oliver syndrome	AD	56	96
PLOD1	Ehlers-Danlos syndrome	AR	30	41
PRKG1	Aortic aneurysm, familial thoracic 8	AD	2	3
SKI	Shprintzen-Goldberg syndrome	AD	20	23
SLC2A10	Arterial tortuosity syndrome	AR	23	34
SLC39A13	Spondylodysplastic Ehlers-Danlos syndrome	AR	2	9
SMAD2	Loeys-Dietz syndrome, congenital heart defects, nonsyndromic	AD	4	13
SMAD3	Aneurysms-osteoarthritis syndrome, Loeys-Dietz syndrome	AD	48	82
SMAD4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, polyposis, juvenile intestinal, Myhre dysplasia, hereditary hemorrhagic telangiectasia	AD	179	143

SMAD6	Craniosynostosis 7	AD	5	38
TGFB2	Loeys-Dietz syndrome	AD	36	38
TGFB3	Loeys-Dietz syndrome (Reinhoff syndrome), arrhythmogenic right ventricular dysplasia	AD	19	26
TGFBR1	Loeys-Dietz syndrome	AD	40	69
TGFBR2	Loeys-Dietz syndrome	AD	58	139
ZDHHC9	Mental retardation, syndromic, Raymond	XL	9	14

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The clinical manifestations of intracranial aneurysms (IA) range from lifelong asymptomaticity to significant morbidity and mortality. IAs are known to aggregate into families and have been linked to several monogenetic and other disorders. This thesis is based on a large population-based database of Eastern Finnish IA patients with an extensive cross-linkage to nationwide registries, offering an exceptional possibility to study IA disease and its disease associations in a familial context.

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