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MINIREVIEW

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The genetics of intracranial aneurysms

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Abstract The rupture of an intracranial aneurysm (IA) leads to a subarachnoid hemorrhage, a sudden onset disease that can lead to severe disability and death. Several risk factors such as smoking, hypertension and excessive alcohol intake are associated with subarachnoid hemorrhage. IAs, ruptured or unruptured, can be treated either surgically via a craniotomy (through an opening in the skull) or endovascularly by placing coils through a catheter in the femoral artery. Even though the etiology of IA formation is mostly unknown, several studies support a certain role of genetic factors. In reports so far, genome-wide linkage studies suggest several susceptibility loci that may contain one or more predisposing genes. Studies of several candidate genes report association with IAs. To date, no single gene has been identified as responsible for IA formation or rupture. The identification of susceptible genes may lead to the understanding of the mechanism of formation and rupture and possibly lead to the development of a pharmacological therapy.

Keywords Intracranial aneurysm · Subarachnoid hemorrhage · Stroke · Genome-wide linkage analysis · Candidate gene

Introduction

Subarachnoid hemorrhage (SAH) is still one of the most sudden and devastating diseases in the field of neurovascular diseases. Its most frequent cause is the rupture of an intracranial aneurysm (IA), which is an outpouching or sac-like widening of a cerebral artery. Initial diagnosis is usually evident on a cranial computer tomography (CT) showing extravasated (hyperdense) blood in the subarachnoid space. In a second step, the gold standard of diagnostic techniques to detect the possible underlying ruptured aneurysm is intra-arterial digital subtraction angiography and additional three-dimensional (3D) rotational angiography (panels A and B in Fig. 1). Recently non-invasive diagnostic imaging modalities are becoming increasingly sophisticated. 3D CT angiography and 3D magnetic resonance angiography allow less invasive methods to reliably depict IAs (see panel C in Fig. 1).

Even though genetic factors are thought to play an important role in the pathogenesis of IA in addition to the well-published environmental factors (Juvela 2002; Wiebers et al. 2003), only recent progress in molecular genetics has enabled us to investigate the possible genetic determinants of this disease. Should it be possible to identify a genetic marker associated with an increased risk of formation and rupture of an IA, the necessity for screening and urgency of treatment could be determined more easily. Although a familial predisposition is the strongest risk factor for the development of IA, the mode of Mendelian inheritance is uncertain in most families. Therefore, multiple genetic susceptibilities are considered to act together in the etiology of IA. Accordingly, researchers applied non-parametric linkage study and case–control association studies for the genetic analysis of IA and thus far identified several genes to be susceptible to IA. Recently, two hypotheses, "common variant–common disease" and "rare variant–common disease," are discussed for the susceptibility of common disease: most likely, both hypotheses are true, dependent on the type of disease. However, the approach to detect the causality is conceptually different in both hypotheses. We summarize the current knowledge of IA genetics and also discuss the method to detect the causalities.

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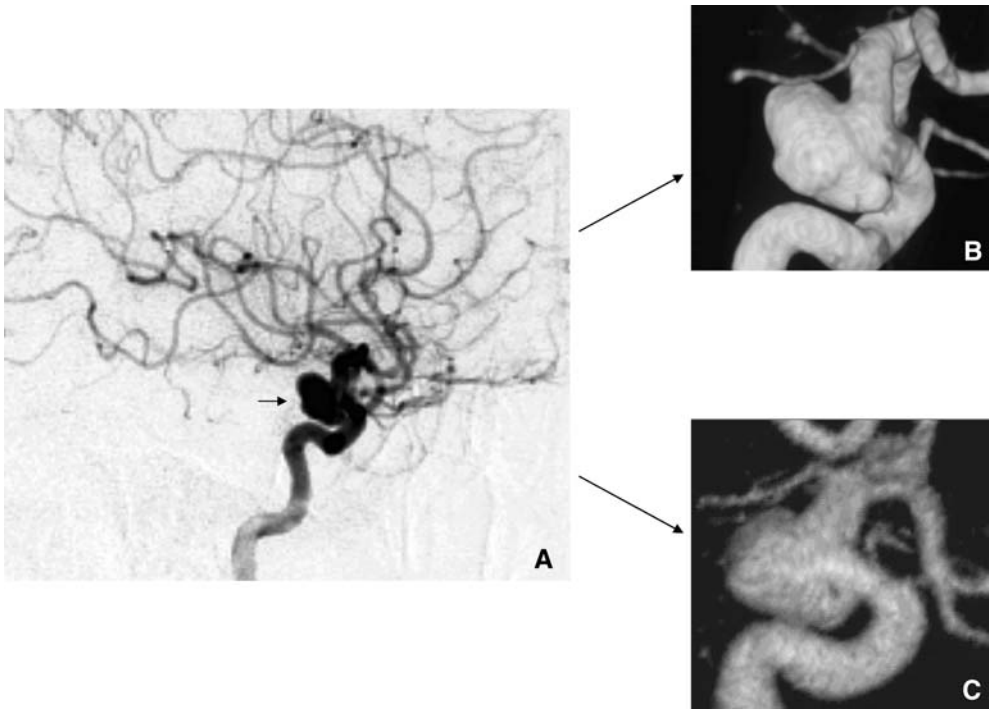


Fig. 1 Imaging of a right internal carotid aneurysm (*arrow*) with **a** a gold standard intra-arterial digital subtraction angiography and **b** a three-dimensional (3D) rotational angiography. **c** A 3D magnetic resonance image, a non-invasive technique, performed with a 3-Tesla MRI depicts the aneurysm at high resolution

Pathology, epidemiology and etiology

Hemodynamic stress at arterial bifurcations are believed to contribute to aneurysm development (Ingebrigtsen et al. 2004). However, it is largely unknown why only some adults develop aneurysms at bifurcations and most do not. A number of contradictory observations led to the dispelling of the hypothesis of a congenital defect of a weak spot in the muscle layer of the arterial wall. Through this, the inner layers of the arterial wall would bulge and then form an aneurysm. But it was demonstrated that these gaps are equally common in patients with and without aneurysms (Stehbens 1989) and usually packed by dense collagen fibrils (Fujimoto 1996; Finlay et al. 1998). Furthermore, the defect in the muscle layer is located in the wall of the aneurysmal sac and not at the neck of the aneurysm (Stehbens 1989). Possibly the influence of the risk factors (mentioned below) leads to a thickening of the intimal layer and subsequently increases strain in the more elastic portions of the vessel wall (Crompton 1966). Structural abnormalities in structural proteins of the extracellular matrix have been identified in the arterial wall at a distance from the aneurysm itself. Computerized morphometric analysis has indicated that reticular fibers in the arterial media of cerebral arteries were significantly decreased in patients with aneurysms. In addition, these fibers were irregularly distributed and shortened when compared to those seen in control arteries (Chyatte et al. 1990). The exact etiology of IA formation remains unclear.

Subarachnoid hemorrhage occurs around 1.6 times more often in women than in men (Rinkel et al. 1998) and 2.1 times more often in blacks than whites (Broderick et al. 1992). Further epidemiological studies demonstrate a strong genetic influence: Siblings have a sixfold increased risk of being struck by the same disease. In total, the risk is three to seven times higher in first-degree relatives of patients with SAH than in the general population (Bromberg et al. 1995; Schievink et al. 1995; Wang et al. 1995; De Braekeleer et al. 1996; Ronkainen et al. 1997). In second-degree relatives, the incidence of SAH is similar to that found in the general population (Bromberg et al. 1995). It has also been shown that the prevalence of unruptured IA is significantly higher (10.5–13.5%) in a Japanese subgroup with a family history of IA (Nakagawa and Hashi 1994; Kojima et al. 1998). The prevalence of harboring an IA within the population aged over 30 years is between 3.6 and 6.5% (Ujiie et al. 1993; Yamaki et al. 1994; Iwamoto et al. 1999; Wardlaw and White 2000). Especially in Japan, where a brain assessment system called "Brain-dock" systematically screens patients for incidental aneurysms, the incidence of unruptured IAs seems to be increasing with the continuous evolution of magnetic resonance angiography imaging techniques (Yoshimoto and Mizoi 1997; Morita et al. 2005). The annual incidence of SAH due to aneurysmal rupture has been reported to be 11/100,000 in the United States (Ingall et al. 1989), whereas the incidence observed in Japan depending on the region is between 14/100,000 (Inagawa et al. 1988) and 96/100,000 (Kiyohara et al. 1989). The risk of rupture depends on the size and location of the aneurysm (White and Wardlaw 2003; Wiebers et al. 2003). It has been reported to be 2.7% per year in a Japanese population (Morita et al. 2005) and 1.9% in a white population (Rinkel et al. 1998).

Treatment

Currently, the two main options of treatment are either microvascular surgical clipping or endovascular coiling of the aneurysm(s). Historically, microsurgical clipping has been the preferred method of treatment. Endovascular treatment has been available as an alternative for the last 15 years (Guglielmi et al. 1991). Multiple platinum coils of various length and diameter are packed into the aneurysm to exclude it from the circulation. Nowadays, depending on the aneurysm's form and location as well as the expertise of the neurointerventionalist and neurosurgeon, the type of treatment is decided on a case-to-case basis.

Identification of the susceptibility gene

The two major approaches—not mutually exclusive, but complementary—are the linkage approach locating the locus of disease using families and the association approach (direct or indirect) identifying a potential disease allele in a case–control design. While linkage analysis is arguably the most powerful method for identifying a locus involving rare, high-risk alleles in Mendelian diseases, many consider genetic association analyses to be the best method for identifying genetic variants related to common and complex diseases, as is the case in IA. The HapMap project, in particular, has made genome-wide association studies the most powerful tool for identification of common alleles to common disease. The recently emerged hypothesis, rare variant–common disease hypothesis, posits that several rare variants in a gene are involved in disease causality of common diseases (Cohen et al. 2004). If this is the case, an association study (even one that is genome-wide with high-density SNP genotyping) would not be able to detect the disease gene because most of the SNPs in the database are common SNPs designed to map common alleles. Therefore, both family-based genetic linkage studies as well as association studies are required for the full understanding of the genetics of IA.

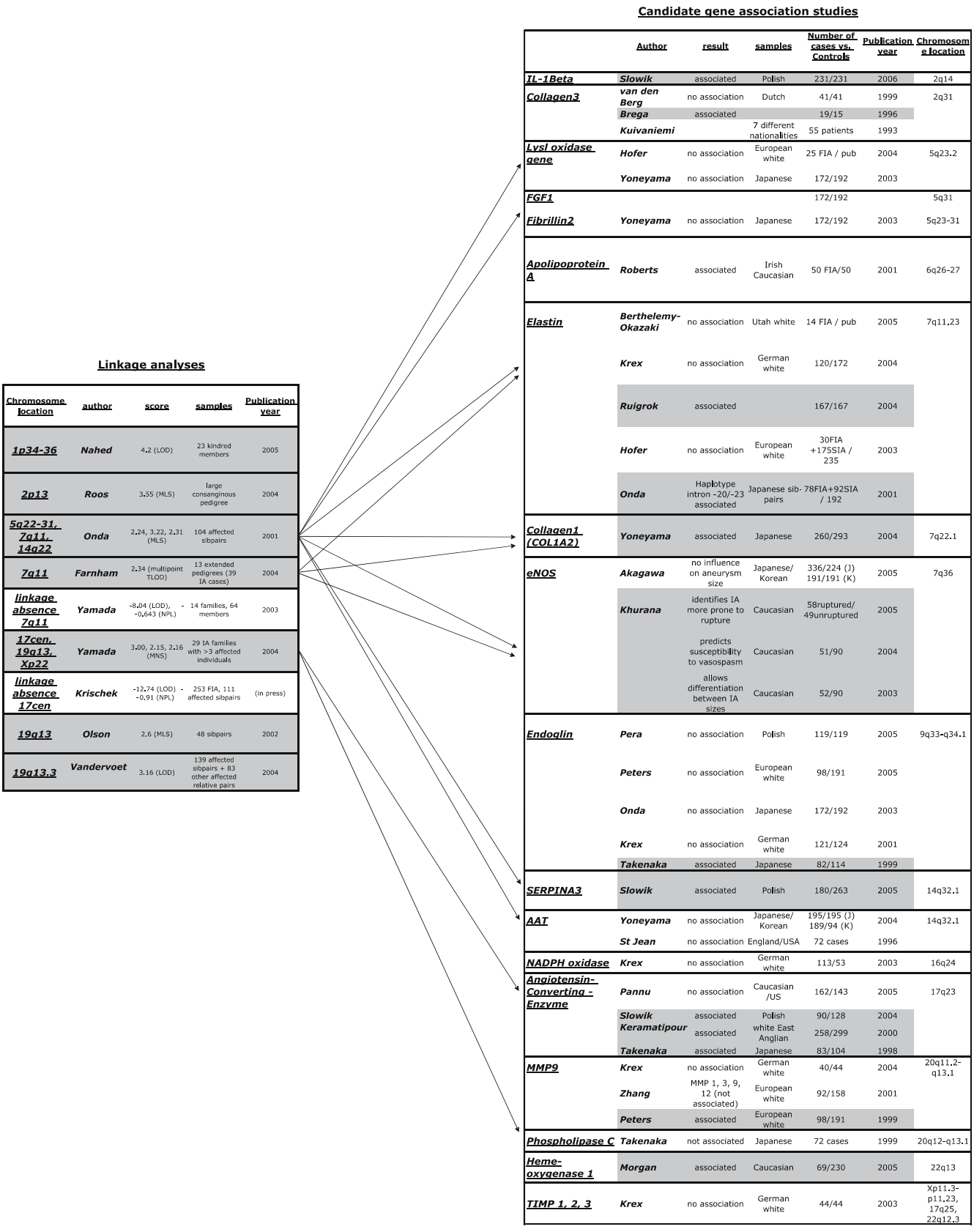
Chromosomal loci mapped by linkage studies

Although the molecular basis of the disorder is not known, family studies strongly support genetic factors in the formation of IA. Several studies of familial aneurysms have identified chromosomal loci showing suggestive evidence of linkage (see Fig. 2). The mode of transmission for harboring an IA is not clear, and the genetics of the disorder appear to be complex, involving multiple loci and interaction of multiple genes (Onda et al. 2001). In accordance with this, several genome-wide scans and linkage studies have identified multiple chromosomal regions (see Fig. 2) that may contain one or more susceptible genes. However, in some cases results cannot be replicated, even when examining patients of the same ethnic background (Onda et al. 2001; Yamada et al. 2003). Onda et al. observed positive evidence of linkage on chromosome 5q22–31 (MLS 2.24), 7q11 (MLS 3.22) and 14q22 (MLS 2.31) with 104 affected sib-pairs. Yamada et al. observed positive evidence of linkage on chromosome 17cen (MLS 3.00), 19q13 (MLS 2.15) and Xp22 (MLS 2.16) with 29 extended families. The inconsistency must be interpreted with caution. Discrepancies are possibly due to genetic heterogeneity and differences of patient cohorts (affected sib-pairs vs. extensive nuclear families). Further studies comprising larger sample sizes are undoubtedly needed, as multiple interacting genes and environmental factors contribute to the phenotype. Two regions that were confirmed in both samples of Japanese and white patients are on chromosome 7q (Onda et al. 2001; Olson et al. 2002) and 19q (Farnham et al. 2004; Yamada et al. 2004) (see Fig. 2). Both regions were verified once using affected sib-pairs and once using extended pedigrees. Alternatively, the rare Mendelian forms of disease might lead to the identification of genes or pathway that plays a key role in the pathogenesis of the common form of the disease. Nahed et al. identified a large family of IA (six living patients and four deceased) showing autosomal dominant inheritance and detected a single locus with a LOD score of 4.2 at chromosome 1p34.3–36.13 (Nahed et al. 2005). Positional (candidate) cloning might be underway in the locus.

A multicenter study of 26 clinical centers, which will enroll a total of 475 families with affected sib-pairs or with multiple affected relatives, has been introduced as the FIA (familial intracranial) study in a recent publication. The investigators' first goal will be to carry out a 10-cM genome screen to identify familial IA susceptibility loci (Broderick et al. 2005). With a sample size of this magnitude, many further studies could lead to meaningful results.

Candidate gene analysis

After identifying several susceptibility loci, the search for a positional candidate gene from such a region would seem to be the logical next step towards identifying those who are predisposed to forming an IA. A host of genes has been looked at although only a few have shown moderate positive association (see Fig. 2). Conflicting results have been obtained, and no single gene has been consistently identified as a candidate gene. Obviously, many case–control studies have also focused on functional genes suspected of being involved in the disease. Of those, some play a role in connective tissue formation, such as collagen, elastin, matrix metalloproteinases and their tissue inhibitors, endoglin, and fibrillin, to name but a few. Considering the genetic role in the formation of IAs, some of the examined genes potentially possess both attributes of function and position (e.g., the elastin gene).



Linkage analyses

Chromosome location	author	score	samples	Publication year
1p34-36	Nahed	4.2 (LOD)	23 kindred members	2005
2p13	Roos	3.55 (MLS)	large consanginous pedigree	2004
5q22-31, 7q11, 14q22	Onda	2.24, 3.22, 2.31 (MLS)	104 affected sibpairs	2001
7q11	Farnham	2.34 (multipoint TLOD)	13 extended pedigrees (39 IA cases)	2004
linkage absence 7q11	Yamada	-8.04 (LOD), -0.643 (NPL)	14 families, 64 members	2003
17cen, 19q13, Xp22	Yamada	3.00, 2.15, 2.16 (MNS)	29 IA families with >3 affected individuals	2004
linkage absence 17cen	Krischek	-12.74 (LOD) - -0.91 (NPL)	253 FIA, 111 affected sibpairs	(in press)
19q13	Olson	2.6 (MLS)	48 sibpairs	2002
19q13.3	Vandervoet	3.16 (LOD)	139 affected sibpairs + 83 other affected relative pairs	2004

Candidate gene association studies

	Author	result	samples	Number of cases vs. Controls	Publication year	Chromosome location
IL-1Beta	Slowik	associated	Polish	231/231	2006	2q14
Collagen3	van den Berg	no association	Dutch	41/41	1999	2q31
	Brega	associated		19/15	1996	
	Kuivaniemi		7 different nationalities	55 patients	1993	
Lysl oxidase gene	Hofer	no association	European white	25 FIA / pub	2004	5q23.2
	Yoneyama	no association	Japanese	172/192	2003	
FGF1				172/192		5q31
Fibrillin2	Yoneyama	no association	Japanese	172/192	2003	5q23-31
Apolipoprotein A	Roberts	associated	Irish Caucasian	50 FIA/50	2001	6q26-27
Elastin	Berthelemy-Okazaki	no association	Utah white	14 FIA / pub	2005	7q11.23
	Krex	no association	German white	120/172	2004	
	Ruigrok	associated		167/167	2004	
	Hofer	no association	European white	30FIA +175SIA / 235	2003	
	Onda	Haplotype intron -20/-23 associated	Japanese sib-pairs	78FIA+92SIA / 192	2001	
Collagen1 (COL1A2)	Yoneyama	associated	Japanese	260/293	2004	7q22.1
eNOS	Akagawa	no influence on aneurysm size	Japanese/ Korean	336/224 (J) 191/191 (K)	2005	7q36
	Khurana	identifies IA more prone to rupture	Caucasian	58ruptured/ 49unruptured	2005	
		predicts susceptibility to vasospasm	Caucasian	51/90	2004	
		allows differentiation between IA sizes	Caucasian	52/90	2003	
Endoglin	Pera	no association	Polish	119/119	2005	9q33-q34.1
	Peters	no association	European white	98/191	2005	
	Onda	no association	Japanese	172/192	2003	
	Krex	no association	German white	121/124	2001	
	Takenaka	associated	Japanese	82/114	1999	
SERPINA3	Slowik	associated	Polish	180/263	2005	14q32.1
AAT	Yoneyama	no association	Japanese/ Korean	195/195 (J) 189/94 (K)	2004	14q32.1
	St Jean	no association	England/USA	72 cases	1996	
NADPH oxidase	Krex	no association	German white	113/53	2003	16q24
Angiotensin-Converting-Enzyme	Pannu	no association	Caucasian /US	162/143	2005	17q23
	Slowik	associated	Polish	90/128	2004	
	Keramatipour	associated	white East Anglian	258/299	2000	
	Takenaka	associated	Japanese	83/104	1998	
MMP9	Krex	no association	German white	40/44	2004	20q11.2-q13.1
	Zhang	MMP 1, 3, 9, 12 (not associated)	European white	92/158	2001	
	Peters	associated	European white	98/191	1999	
Phospholipase C	Takenaka	not associated	Japanese	72 cases	1999	20q12-q13.1
Heme-oxygenase 1	Morgan	associated	Caucasian	69/230	2005	22q13
TIMP 1, 2, 3	Krex	no association	German white	44/44	2003	Xp11.3-p11.23, 17q25, 22q12.3

Fig. 2 Overview of genetic studies of intracranial aneurysms: the *table on the left side* shows linkage studies. *Gray background* indicates chromosomal loci found. *Right-hand table* shows candidate gene association studies. *Gray background* if positive association was found. *Arrows* connect locations on the same chromosome. *LOD* Logarithm of odds, *MLS* maximum LOD, *TLOD* theta LOD, *NPL* non-parametric linkage analysis, *MNS* / *Emphasis> maximum non-parametric logarithm of the odds, FIA* familial intracranial aneurysm, *SIA* sporadic intracranial aneurysm

An example of conflicting results are the studies concerning the endothelial nitric oxide synthase (eNOS) gene. One study group concluded that a polymorphism of the eNOS gene correlates with the aneurysm's size, observed in Caucasian patients (Khurana et al. 2003). But this could not be replicated in a study using DNA samples of Japanese patients (Akagawa et al. 2005). It was also reported that three polymorphisms of this gene make it possible to single out patients with IAs that are more prone to rupture, comparing 58 ruptured to 49 unruptured IA cases of Caucasian origin (Khurana et al. 2005). Again, this could not be verified in a study consisting of 297 ruptured and 109 unruptured aneurysm cases of Japanese patients performed at the authors' institute (data not yet published).

As summarized in Fig. 2, thus far numerous association studies have been performed, some showing positive associations, some negative. But the majority of studies only examined small sample sizes and thus are mostly preliminary.

Among the genes that could be replicated, the elastin gene, which is located on chromosome 7q11, appears to be a highly likely candidate involved in the formation of IAs. It is located in a region that was suggestive of linkage in both Japanese and white patients from Utah (7q11). In an unpublished study, functional analysis showed the alteration of gene expression of elastin in familial IA patients.

Environmental factors

A recent meta-analysis of all longitudinal and case–control studies for risk factors for SAH from 1966–2005 concluded environmental risk factors to be smoking (relative risk 2.2, odds ratio 3.1) and excessive alcohol consumption (relative risk 2.1, odds ratio 1.5). A further risk factor is hypertension, showing a relative risk of 2.5 and odds ratio of 2.6. Interestingly a less robust risk factor was non-white ethnicity (relative risk 1.8, odds ratio 3.4) (Feigin et al. 2005).

Although it has still not been established whether the impact is the same as in abdominal aneurysms (Alexander 2004), inflammatory and immunological reactions may also be related to IA formation and rupture. Immunohistochemistry studies showed elevated levels of immunoreactive components in IA tissue as compared to controls (Chyatte et al. 1999; Takagi et al. 2002). A recently published hypothesis proposed that decreases in both circulating estrogen levels and cerebrovascular estrogen receptor density may contribute to an increased risk of IA pathogenesis and rupture in women during and after menopause (Harrod et al. 2006).

Associations with other disorders

Connective-tissue disorders such as polycystic kidney disease, the Ehlers-Danlos syndrome (EDS), pseudoxanthoma elasticum and fibromuscular dysplasia are associated with the presence of IA and subarachnoid hemorrhage (Schievink et al. 1994). The relative risk is increased for a ruptured aneurysm in the classic and vascular types of EDS (type I/II and IV) and autosomal dominant polycystic kidney disease (ADPKD1 and ADPKD2) (Watnick et al. 1999; Nekrysh 2000; Hademenos et al. 2001). IAs occur in about 8% of ADKPD patients (Gibbs et al. 2004) and recur frequently in ADKPD patients with known aneurysms, particularly if there is a positive family history (Ruggieri et al. 1994; Belz et al. 2003).

Grond-Ginsbach et al. found connective tissue alterations in skin biopsies of 7 (out of 21) patients with IAs. The abnormalities resembled those of EDS types II and IV, although they showed no clinical signs of a known connective-tissue disorder (Grond-Ginsbach et al. 2002).

Concluding remarks

Intracranial aneurysms are cerebrovascular diseases that can cause catastrophic subarachnoid hemorrhages. Several linkage regions and candidate genes showing association have been reported. Aside from genetic factors, environmental factors such as hypertension, smoking and alcohol intake are related to the pathogenesis and eventual rupture of IAs.

A single gene disorder does not seem to be involved, and a complex etiology involving multiple loci is proposed. Possibly this disease is caused by many different genes. Identification of predisposing genes may lead to a better understanding of the mechanism of IA formation. It may also allow a prediction of which individuals may be susceptible to developing an IA. Further multicenter studies comparing cohorts of patient samples of different ethnicity have to be carried out. Additional genome-wide scans as well as candidate gene association studies may narrow down the responsible genetic factors and help in understanding the pathomechanism of IA formation.

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