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REVIEW

Cerebrovascular disorders associated with genetic lesions

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Abstract
Cerebrovascular disorders are underlain by perturbations in cerebral blood flow and abnormalities in blood vessel structure. Here, we provide an overview of the current knowledge of select cerebrovascular disorders that are associated with genetic lesions and connect genomic findings with analyses aiming to elucidate the cellular and molecular mechanisms of disease pathogenesis. We argue that a mechanistic understanding of genetic (familial) forms of cerebrovascular disease is a prerequisite for the development of rational therapeutic approaches, and has wider implications for treatment of sporadic (non-familial) forms, which are usually more common.

Keywords Cerebrovascular disease · Hemorrhagic cerebrovascular disease · Small vessel disease · Genetics · Model organisms

Introduction

Homeostatic signaling between neuronal, glial, and vascular compartments (the "neurovascular unit") within the adult brain is of fundamental significance for normal physiological functions of the central nervous system (CNS) [1]. The importance of interactions between different cell types is indeed already evident during development, exemplified by the orchestrated interplay between neural and vascular progenitors [2, 3]. Disruptions in neurovascular development lead to diverse disorders underlain by abnormalities in blood vessel structure and perturbations in cerebral blood flow, which is critical for proper neuronal function [4–7].

In this review, we provide a brief history and summarize our current understanding of cerebrovascular diseases that have been clearly associated with underlying genetic lesions (Table 1). Rapidly evolving molecular genetic methodologies led to the identification of causative genes for a wide spectrum of cerebrovascular diseases involving both large- and small-sized vessels, offering the opportunity to investigate the underlying mechanisms using model organisms and in vitro assays [8–11]. We connect current genomic findings with analyses aiming to elucidate the cellular and molecular mechanisms of disease pathogenesis in an attempt to understand how specific genetic lesions cause diverse prototypes of cerebrovascular disorders. We argue that a mechanistic understanding of genetic (familial) cerebrovascular disease is a prerequisite for the development of rational therapeutic approaches, and has wider implications for treatment of sporadic (non-familial) forms, which are usually more common. When applicable, we discuss possible methodological improvements that could advance our understanding of these abnormalities, as well as therapeutic strategies informed by current findings.

Hereditary hemorrhagic cerebrovascular disease

The first known case of a cerebrovascular lesion, a berry-like growth within the frontal lobe, was described in 1854 by von Luschka [12]. More than 70 years later, Cushing [13] and Dandy [14, 15] independently reported extensive series of cerebrovascular malformations, which were subsequently classified into distinct histopathological subtypes (telangiectasias, cerebral cavernous malformations, venous malformations, and arteriovenous malformations) [16, 17]. These occur with a high prevalence (initially estimated to be 4–6% [18–20], but approximately 3% in more recent population-based brain magnetic resonance imaging [MRI] studies

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Table 1 Cerebrovascular diseases and associated genes

Disease	Gene	Chromosome	Inheritance	Function	References
Hemorrhagic disease					
CCM	*CCM1/KRIT1*	7q	AD	Controlling endothelial barrier junctions	Laberge-le Couteulx et al. [44]
	CCM2	7p	AD	Controlling endothelial barrier junctions	Liquori et al. [45] Denier et al. [46]
	CCM3/PDCD10	3q	AD	Induction of apoptosis; broadly expressed	Bergametti et al. [47] Guclu et al. [48]
IA	*SOX17*	8q	–	Maintenance of arterial integrity	Bilguvar et al. [139] Yasuno et al. [140]
	CDKN2A-B	9p	–	Cell growth regulator	Bilguvar et al. [139] Yasuno et al. [140] Leeper et al. [145]
	CNNM2	10q	–	Unknown	Yasuno et al. [140]
	KL/STARD13	13q	–	Unknown/cell proliferation	Yasuno et al. [140]
	RBBP8	18q	–	Cell cycle progression	Yasuno et al. [140]
	EDNRA	4q	–	Vasoconstriction	Yasuno et al. [141]
MMD	*RNF213*	17q	AD	Angiogenic response to inflammation	Kamada et al. [159] Liu et al. [160]
	GUCY1A3	4q	AR	Subunit of the major NO receptor in the vascular wall	Herve et al. [169]
	BRCC3	Xq	XR	Proper angiogenesis	Miskinyte et al. [170]
Small vessel disease					
CADASIL	*NOTCH3*	19q	AD	Cell fate; stability of vascular smooth muscle cells	Joutel et al. [182]
CARASIL	*HTRA1*	10q	AR	Serine protease; regulation of TGFβ signaling	Hara et al. [183]
CAA	*APP*	21q	AD	Multiple; primary function unknown	Rovelet-Lecrux et al. [245]
	BRI2	13q	AD	Unknown	Vidal et al. [253]
	CST3	20p	AD	Cysteine protease inhibitor	Ghiso et al. [249]
	TTR	18q	AD	Transportation of thyroxine and retinol-binding protein	Brett et al. [250]
	GSN	9q	AD	Actin filament dynamics	Ghiso et al. [251]
CRV	*TREX1*	3p	AD	Maintenance of vascular integrity	Richards et al. [184]

List of diseases, associated genes with chromosomal localization, pattern of inheritance, function of encoded proteins, and main references are given

AD, autosomal dominant; *APP*, amyloid precursor protein, AR, autosomal recessive; *BRCC3*, BRCA1/BRCA2-containing complex subunit 3; *BRI2*, integral membrane protein 2B; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CCMs, cerebral cavernous malformations; *CDKN2A-B*, cyclin-dependent kinase inhibitor 2A-B; *CNNM2*, cyclin M2; CRV, cerebroretinal vasculopathy; *CST3*, cystatin C; *EDNRA*, endothelin receptor type A; *GSN*, gelsolin; *GUCY1A3*, guanylate cyclase soluble subunit alpha-3; *HTRA1*, high-temperature requirement A serine peptidase 1; *IA*, intracranial aneurysms; *KL/STARD13*, Klotho/StAR related lipid transfer domain containing 13; *KRIT1*, Krev1 interaction trapped gene 1; MMD, Moyamoya disease; *NOTCH3*, neurogenic locus notch homolog protein 3; *PDCD10*, programmed cell death protein 10; *RBBP8*, retinoblastoma binding protein 8; *RNF213*, ring finger protein 213; *SOX17*, SRY-related HMG-box family member 17; *TTR*, transthyretin; *TREX1*, three prime repair exonuclease 1; XR, X-linked recessive

[21]) around the globe in all ethnicities, and although they are most often sporadic, familial forms are not infrequent.

Cerebral cavernous malformations (CCMs)

CCMs are common cerebrovascular lesions, also termed cavernomas, in the CNS and, rarely, the retina, with an estimated prevalence of 0.3–0.9% on the basis of large prospective autopsy studies, clinically-based and population-based brain MR images [18, 21–29]. Cavernomas are collections of enlarged, densely packed vascular sinusoids with an abnormal structure lined with a single layer of endothelial cells, lack vessel wall elements, and are embedded in a collagen matrix without intervening brain parenchyma [16, 17]. They can be found in all brain regions and are usually 1–5 cm in size. Due to their primitive vessel architecture and low-pressure blood flow, CCMs tend to leak, causing microhemorrhages and subsequent hemosiderin deposition, leading to a typical MRI signature [30–32] (Fig. 1a). Although mostly clinically silent, depending on location and size, the lesions can cause a broad range of symptoms, including headache, seizures, and focal neurological deficits. A fraction of patients with CCM experience catastrophic, potentially fatal, cerebral hemorrhages [23, 25, 26, 33–35]. Treatment options include observation of asymptomatic lesions, antiepileptic medication, surgical excision of accessible lesions in patients with symptomatic hemorrhage or intractable seizures, and radiosurgery; however, pharmacological therapies that improve outcome are not available.

Both sporadic (more common) and hereditary forms of CCM exist; sporadic lesions are typically solitary [36], whereas familial CCM is characterized by multiple lesions in the setting of a strong family history (Fig. 1b). The hereditary nature of CCM was recognized as early as 1928, when Kufs described a father and daughter presenting with cerebral, retinal, and cutaneous cavernous malformations [37]. Genetic linkage analyses performed in the 1990s mapped three CCM loci, and subsequent efforts identified the causative genes: *CCM1/KRIT1* (on chromosome 7q), *CCM2* (7p), and *CCM3/PDCD10* (3q) [38–49]. Loss of function mutations in these three genes account for 98% of familial CCM disease [8, 17, 50], and although they are generally thought to lead to clinically and radiographically similar disease, familial CCM associated with *CCM3* mutations is characterized by exceptionally aggressive clinical phenotypes, greater lesion burden, and more frequent hemorrhages earlier in life [51, 52]. At least some cases of sporadic CCM also involve somatic mutations in these same genes [53]. A single case involving a large genomic rearrangement was recently reported in familial CCM2 [54].

Familial CCM is characterized by autosomal-dominant mode of inheritance and high but incomplete penetrance, estimated to be 53% for *CCM1*, 19% for *CCM2*, and 16% for *CCM3* [55, 56]. Knudson's two-hit hypothesis, according to which one mutational event is inherited in the form of a germline mutation, whereas a second is acquired in a subset of somatic cells [57], has been employed to explain CCM inheritance [58–61]. The non-homologous, cytoplasmic CCM proteins (CCM1/KRIT1, CCM2, and CCM3) are expressed in the arterial endothelium in many tissues and organs and are critical for vascular development [62–65]. In addition to endothelial cells, the CCM proteins are expressed in neurons and glia [66–68], an observation potentially also related to the finding that CCM lesions form almost exclusively within the central nervous system [69]. In the setting of treatment, it is necessary to screen for the patient's family history, as numerous families with CCM have been reported around the globe [43, 70, 71] and in various ethnic populations [71, 72]. The first study describing clinical and radiographic features for 13 Hispanic American families with CCM [72] was indeed published in 1998, accompanied in the same year by the first large series of Caucasian non-Hispanic patients with familial CCM [71]. These and other studies demonstrated that, in contrast to only 10–20% of other ethnic groups, as many as 50% of Hispanic Americans, a population with a strong founder mutation [73, 74], have a first-degree relative with CCM.

The CCM proteins have essential roles in angiogenesis and cardiovascular development and are required for endothelial cell integrity [63–65, 75–80]. In mice, conditional knockout of individual *Ccm* genes in endothelial cells at early postnatal stages results in acute CCM disease, characterized by vascular malformations in the retina and the cerebellum, two organs undergoing intense postnatal angiogenesis [64, 77, 81–83]. The CCM proteins are also expressed in neurons and astrocytes [66–68], where their role remains largely unknown. CCM3 appears to have critical functions not only in endothelial cells, where it has been implicated in stabilization of VEGFR2 signaling and regulation of angiopoietin 2 exocytosis [65, 84], but also in neural cells. CCM3 is required for neuronal migration and, indirectly, for cerebrovascular development, with its loss from the neural lineage leading to simplified vascularity, diffuse vessel dilation, and cerebrovascular malformations that resemble cavernomas [85, 86]. The emerging role of CCM3 in non-vascular cells implies it functions in multiple components of the neurovascular unit and may help explain why cavernomas, in humans and model organisms alike, only develop within neural context (CNS and retina), despite widespread expression of the CCM proteins in endothelial cells of most organs, where they play critical roles, as demonstrated by the impact of *Ccm* gene inactivation in model organisms.

The cellular and molecular mechanisms by which CCM protein loss leads to lesion formation remains an active area

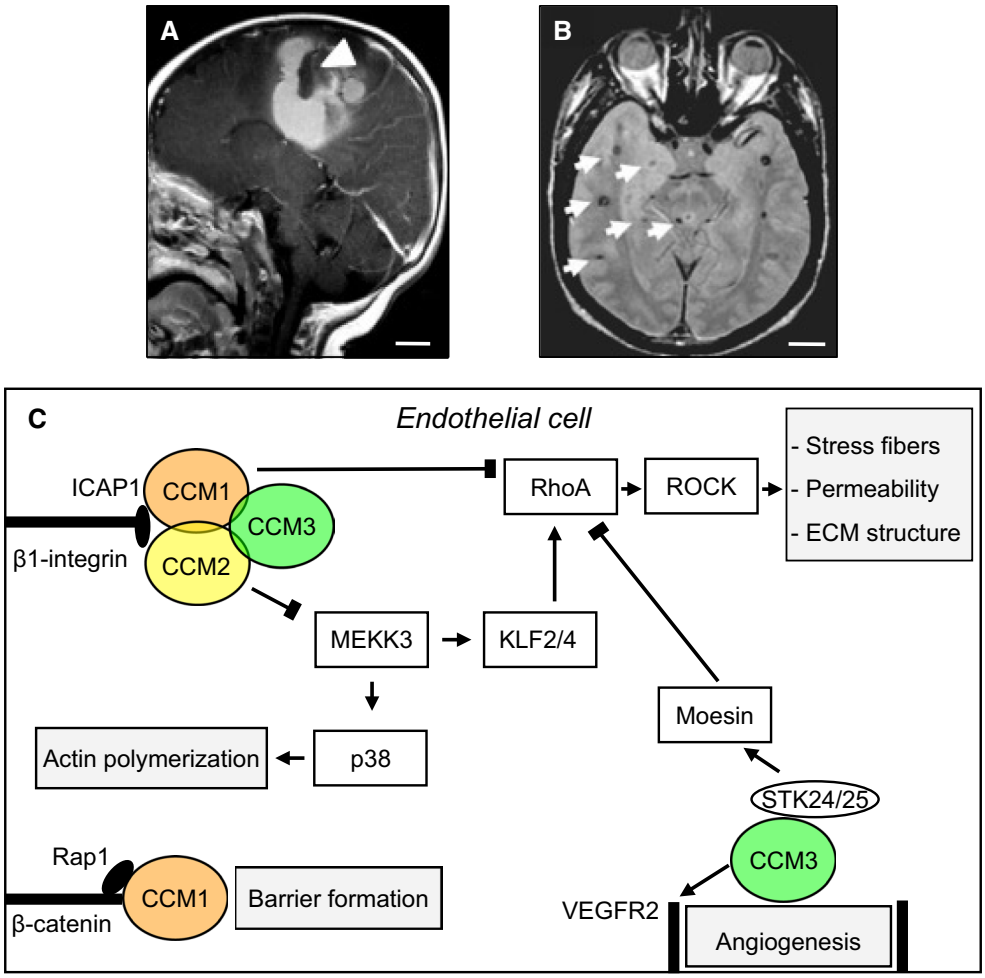

Fig. 1 Cerebral cavernous malformations (CCMs). **a** Sagittal magnetic resonance (MR) imaging shows a large cavernoma (arrowhead) with a resultant gross hemorrhage. **b** Axial MR image of a patient with the genetic form of CCM demonstrates multiple small lesions with a characteristic hemosiderin ring surrounding them (arrows). Scale bars (**a**, **b**): 2 cm. Images courtesy of Dr. Murat Gunel (Department of Neurosurgery, Yale School of Medicine and Yale New Haven Hospital). **c** Summary of select interactors, intracellular pathways, and cellular processes that have been associated with the CCM proteins. The three CCM proteins maintain endothelial function and control angiogenesis. CCM1, CCM2, and CCM3 form a trimeric complex with the scaffolding protein CCM2 acting as a hub. All CCM proteins have an antagonistic effect on the RhoA/ROCK signaling pathway mediated by distinct interactors (arrow-headed lines: activation; bar-headed lines: inhibition). RhoA/ROCK pathway activation in the absence of CCM proteins results in stress fiber formation, increased vascular permeability (possibly explaining why lesions in patients tend to leak causing microhemorrhages) of CCM, and alters the composition of the extracellular matrix (ECM). CCM1 interaction with ICAP1 inhibits β1-Integrin activation and supports Rap1-mediated stabilization of endothelial junctions, thereby contribution to barrier formation. CCM2 interaction with MEKK3 results in decreased p38 activity to modulate actin polymerization. CCM3 stabilizes VEGFR2 signaling to regulate angiogenesis and negatively regulates Rho via its direct interactors STK24/25, which activate moesin. CCM: cerebral cavernous malformation. ECM: extracellular matrix. ICAP1, integrin cytoplasmic domain-associated protein 1; KLF2/4, Krüppel-like factor 2/4; MEKK3, mitogen-activated protein kinase kinase kinase 3; Rap1, Ras-associated protein 1; RhoA, Ras homolog gene family, member A; ROCK, Rho-associated coiled-coil kinase; VEGFR2, vascular endothelial growth factor receptor 2

of investigation. Recent, occasionally conflicting, findings have contributed to our understanding of the pathogenesis of CCM, and accumulating knowledge of CCM protein interactors might help to elucidate CCM disease pathophysiology. The CCM proteins can be found in a dynamic trimeric complex, with CCM2, a scaffolding protein, acting as the hub and interacting directly with CCM1 and CCM3; however, each also interacts with a variety of other signaling, cytoskeletal, and adaptor proteins [60, 87, 88] (Fig. 1c). Several direct interactors for each of the CCM proteins have been identified, including, for CCM1, the small GTPase RAP1, the membrane anchor protein heart of glass 1 (HEG1) [89], and the integrin cytoplasmic domain-associated protein-1 (ICAP1) [90, 91]; for CCM2, MAPK/ERK kinase

kinase-3 (MEKK3) (leading to p38 activation) [92, 93]; and for CCM3, the three Germinal Center Kinase III (GCKIII) serine/threonine (STE20) kinases STK24 and STK25 (via which CCM3 interacts with moesin), and MST4, as well as the scaffolding proteins paxillin and striatin (Fig. 1c) [94–100]. Of all these bona fide interactors, MEKK3 [92, 93, 101–104] has emerged as a key player in the formation and progression of CCM lesions. Gain of MEKK3 signaling and upregulation of its targets, the transcription factors KLF2 and KLF4, have been causally linked to CCM pathogenesis and onset and progression of lesions [105–107], preceding endothelial-to-mesenchymal transition underlain by changes in TGF-β/BMP signaling sensitivity [82, 108, 109]. Additional work will be needed to fully elucidate lesion formation at the cellular and molecular level.

What remains well-established, yet mechanistically not fully understood, is that CCM protein disruption leads to a common biochemical defect: activation of the small GTPase RhoA, consistent with early proteomic studies suggesting CCM involvement in cytoskeletal regulation (Fig. 1c) [101]. RhoA activation is a common outcome of CCM protein modulation in cell culture and model organisms [75, 78, 85, 86, 110–115], as well as in surgically resected familial and sporadic CCM lesions [53, 112, 116]. Although the mechanistic relationships leading to RhoA-ROCK activation are still being investigated, they have inspired attempts to explore pharmacological inhibition of RhoA-ROCK signaling as a potential therapeutic strategy for symptomatic CCM patients [111, 117]. A handful of candidate drugs with variable effects have been identified in studies involving cell culture and preclinical models: (a) fasudil, a ROCK inhibitor (approved in Japan and China but not in the US or Europe), which reduces vascular leakiness in *Ccm1* and *Ccm2* heterozygous mice and lesion burden in a chronic, sensitized model of CCM1, but not CCM2, disease [112, 114, 118]; (b) simvastatin, which stabilizes the endothelium of *Ccm2* heterozygous mice [75], yet does not reduce lesion burden in acute (inducible) or chronic models of CCM1 or CCM2 [118, 119]; (c) cholecalciferol (vitamin D3) and tempol (scavenger of superoxide), two repurposed drugs, which decrease lesion burden in an acute model of CCM2 [119]; and (d) the anti-inflammatory drugs sulindac sulfide and sulindac sulfone, which decrease lesion burden in an acute model of CCM3 [120]. More recent findings suggested that sustained inhibition of the mevalonate pathway by inhibition of HMG-CoA reductase and prenylation (respectively, by fluvastatin and the *N*-bisphosphonate zoledronic acid) is effective in chronic and acute models of CCM3 [83]. It should be noted, however, that these candidate drugs have yet to be tested across all three CCM models, and thus, whether they are broadly effective, even in model organisms, remains an open question.

Intracranial aneurysms (IAs)

IAs are localized vascular bulges that typically form along cerebral arteries due to weakening of the vessel wall, which can become unstable at branch points and eventually dissect (Fig. 2a–c). Rupture of saccular IAs accounts for about 80% of cases of subarachnoid hemorrhage, and is associated with high mortality: many individuals do not survive the first few days after the event, and around 50% die within a month [121, 122]. IA is a multifactorial disorder of poorly understood etiology. Both IA-specific (size, location) and patient-related (smoking, high blood pressure, excessive alcohol consumption, female gender) risk factors are associated with aneurysm rupture [9, 123, 124]. In addition, there is a clear genetic predisposition for IA formation and rupture, first noted in the 1950s with the description of confirmed aneurysms in two members of the same family [125] and receiving increasing attention in the 1960s [126–128]. A number of systemic heritable disorders are frequently associated with IA, namely autosomal-dominant polycystic kidney disease (ADPKD), Ehlers–Danlos syndrome (EDS), Marfan syndrome (MFS), Alagille syndrome, and neurofibromatosis type 1 [129–132]. In particular, the connective-tissue disorder EDS is frequently associated with IA rupture underlain by systemic vessel wall instability. Efforts to elucidate the complex genetics of saccular IA date to 2001 [133, 134]. Although early candidate gene and small case–control studies were not particularly successful, family-based genome-wide linkage analyses identified a large number of significant, very rare variants [135–138], but still not a susceptibility gene, most likely due to complex inheritance patterns of the variants, as well as genetic heterogeneity. On the other hand, population-based, large genome-wide association studies detected numerous single-nucleotide polymorphisms (SNP) as risk factors for IA formation or rupture. These variants occur in a large number within patient cohorts, whereas each polymorphism carries just a small risk for disease development. Nonetheless, the sum of these variants may increase the disease risk dramatically. Intriguingly, the SNPs often map within genomic regions encoding proteins important for connective tissue stability or metabolic vessel function. These genomic loci, including namely *SOX17*, *CDKN2A-CDKN2B*, *CNNM2*, *EDNRA, KL/STARD13*, and *RBBP8* [139–142], have been linked to other vascular disorders (e.g., *EDNRA* to migraine headaches [143]). In line with these findings, deletion of *Sox17* or *Cdkn2b* in the mouse results in aneurysm-like arterial dilatations in the cerebral vasculature [144, 145].

Although these findings strongly suggest a genetic basis in IA formation and rupture, no diagnostic test for studying specific genetic risk factors neither for IA development

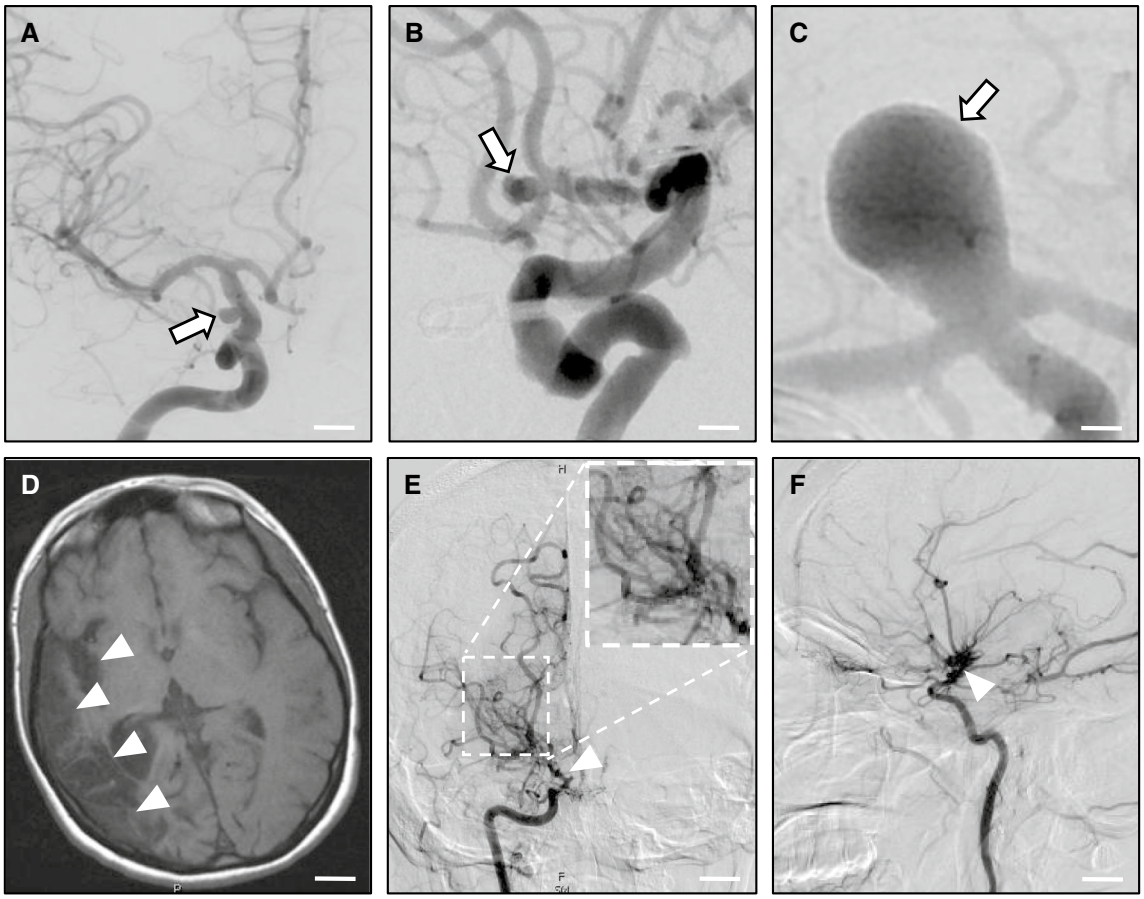

Fig. 2 Intracranial aneurysms (IA) and Moyamoya disease (MMD). **a**–**c** Intracranial aneurysms. Computed tomography (CT) angiography studies demonstrate cerebral aneurysms (arrows) of the supraclinoid portion of the internal carotid artery (**a**); the anterior communicating artery (**b**); and the basilar artery (**c**). Scale bars: **a** 0.7 cm; **b** 0.5 cm; **c** 0.2 cm. **d**–**f** Moyamoya disease. MR imaging (**d**) shows right-sided encephalomalacia (loss of brain tissue after repeated strokes; arrowheads) above the middle cerebral artery, arising from stenosis/occlusion of the right internal carotid artery. Anterior–posterior (**e**) and lateral (**f**) CT angiography reveals occlusion of the right internal carotid artery (arrowhead) with a 'puff-of-smoke' network of collateral vessels (inlay in E). Scale bars: **d** 2 cm; **e**, **f** 1.3 cm. Images courtesy of Drs. Charles Matouk and Branden Cord (Department of Neurosurgery, Yale School of Medicine and Yale New Haven Hospital)

nor for IA rupture risk has been established. A larger number of IA cases will have to be studied in multi-center efforts to distinguish between background mutation in the individual [146] and aneurysm-causing aberrations, to improve our understanding of IA formation and rupture.

Moyamoya disease (MMD)

MMD is clinically characterized by repetitive ischemic strokes caused by spontaneous occlusions of the circle of Willis, a circulatory anastomosis localized at the cerebral base that supplies large parts of the brain with blood (Fig. 2d–f). MMD was first described in 1969 [147] in Japan and indicates an isolated cerebral angiopathy; syndromic Moyamoya is associated with additional conditions. Underlying MMD is a progressive stenosis within the distal internal carotid artery in the anterior circle of Willis, leading to development of numerous compensating collaterals, the so-called 'moyamoya' vessels ('moyamoya' is a Japanese mimetic word describing the 'puff of smoke' appearance of collateral vessels on conventional X-ray angiography). Clinical features differ considerably in pediatric and adult patients and include cerebral ischemia in children, and cerebral hemorrhage in adults (although ischemia has been reported in non-Asian adults) [148, 149].

MMD is more common in Far East countries, especially Japan and Korea, with about 16.1 in 100,000 individuals affected in endemic areas [150], where it represents the most common pediatric cerebrovascular disease, with a prevalence of 3 per 100,000 children [151]. Recently, however, the number of diagnosed patients in Europe and North America has been increasing [152]. Environmental factors were once thought to cause MMD [153], yet the personal MMD risk of individuals emigrating from high to low incidence areas [154, 155], considered together with global distribution patterns and the identification of familial forms, strongly

suggest a genetic contribution. This notion is supported by findings that MMD is a systemic, rather than brain-limited, disease [156]. Familial forms of MMD appear to have variable, i.e., autosomal-dominant, autosomal-recessive, or X-linked, inheritance.

Autosomal-dominant MMD with incomplete penetrance has been linked to a locus on chromosome 17q25.3 in Japanese families, and subsequently confirmed in additional populations [157, 158]. Linkage analysis and genome-wide association studies demonstrated significant association between MMD and a variant (R4810K) of RNF213, a ring finger protein with ubiquitin ligase and ATPase activities [159–162]; this variant has not been reported in Caucasian populations yet, suggesting variability in the genetic landscape [163]. RNF213 plays a role in angiogenic and inflammatory responses of endothelial cells [160, 164]. Of interest, homozygosity for the R4810K variant leads to MMD with extracranial systemic vasculopathy [165]. Given that around 80% of Japanese MMD patients harbor susceptibility variants of *RNF213*, 17q25.3 is considered a major disease locus [159, 161], however, the lack of a cerebrovascular phenotype in *Rnf213* knockout mice and high prevalence of *RNF213* variants in healthy control populations suggest multifactorial etiology [166]. On the other hand, autosomal-recessive MMD with achalasia has been associated with mutations in *GUCY1A3* (4q32.1) [167], encoding a subunit of the main receptor for nitric oxide (NO) [168]. In addition, syndromic MMD displaying X-linked recessive inheritance [169] has been associated with loss of *BRCC3* (Xq28), a gene essential for angiogenesis [170]. Finally, MMD with no strictly defined pattern of inheritance has been associated with numerous other loci [171–176]. The most recently identified candidate gene, *CCER2* on chromosome 19, has been proposed as a potential biomarker of MMD due to brain-specific expression [177]. Additional insight into MMD will be obtained by establishing and investigating patient-derived cell lines and by analysis of coding as well as non-coding RNA, which could also provide potential therapeutic targets [178–180].

Hereditary cerebral small vessel disease (SVD)

Cerebral SVD represent a heterogeneous group of disorders, common in the elderly, that predispose to ischemic or hemorrhagic events, often with white matter, or almost exclusively leptomeningeal, involvement. Clinically, these vascular diseases result in progressive cognitive decline [181]. A minor part of cerebral SVD, including cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [182]; cerebral autosomal-recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) [183]; autosomal-dominant retinal vasculopathy with cerebral leukodystrophy [184]; brain SVD with hemorrhage (Collagen 4–related disorder) [185]; familial cerebral amyloid angiopathy (CAA) [186, 187]; and cerebroretinal vasculopathy (CRV) [188], are hereditary and have been associated with specific genetic lesions. Below we review a subset of hereditary cerebral SVD, with emphasis on those most prevalent, extensively studied in patients, and modeled in the laboratory.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

In 1977, Sourander and Walinder reported a hereditary multi-infarct dementia with autosomal-dominant mode of inheritance in multiple members of a three-generation family [189, 190]. About 20 years earlier, van Bogaert had described a progressive subcortical encephalopathy in two sisters [191], which was verified much later by genetic analysis of old tissue specimens as the first family reported with this condition. Often manifesting in early adulthood, but also increasingly recognized as a disease of late onset and milder course [192–194], CADASIL is characterized by small subcortical infarcts, and underlain by arterial and arteriolar changes leading to vascular cognitive impairment and migraine with aura (Fig. 3a). The disease locus was mapped to chromosome 19q12 [195] and a few years later dominant mutations in *NOTCH3* were identified in patients with CADASIL [182]. This discovery linked for the first time the Notch signaling pathway with hereditary disease. CADASIL is now recognized as the most common monogenic form of hereditary ischemic stroke. To date, more than 500 families with the disease have been identified worldwide (the majority in Europe), with more than 230 unique mutations reported (Human Genetic Mutation Database website, www.hgmd.cf.ac.uk), but a clear genotype–phenotype correlation has still to emerge [196, 197]. Mutations mapping to EGF repeats 1–6 have been associated with higher lesion load on MRI, possibly predisposing to a more severe form of the disease [198].

The overall prevalence of CADASIL is unknown (it is estimated to be 1–2/50,000 but likely remains underdiagnosed) [199, 200] and, in addition to the hereditary forms, rare sporadic cases have been reported [201, 202], as have homozygous patients with phenotypes not different from heterozygotes [203–207]. The clinical presentation varies, and includes subcortical ischemic events, cognitive impairment and dementia, migraine with aura (an initial clinical sign in 20–30% of patients), mood disturbances and apathy [192, 208]. Currently, there is no treatment of proven efficacy. The arteriopathy affects mainly the small penetrating cerebral and leptomeningeal arteries and is characterized by

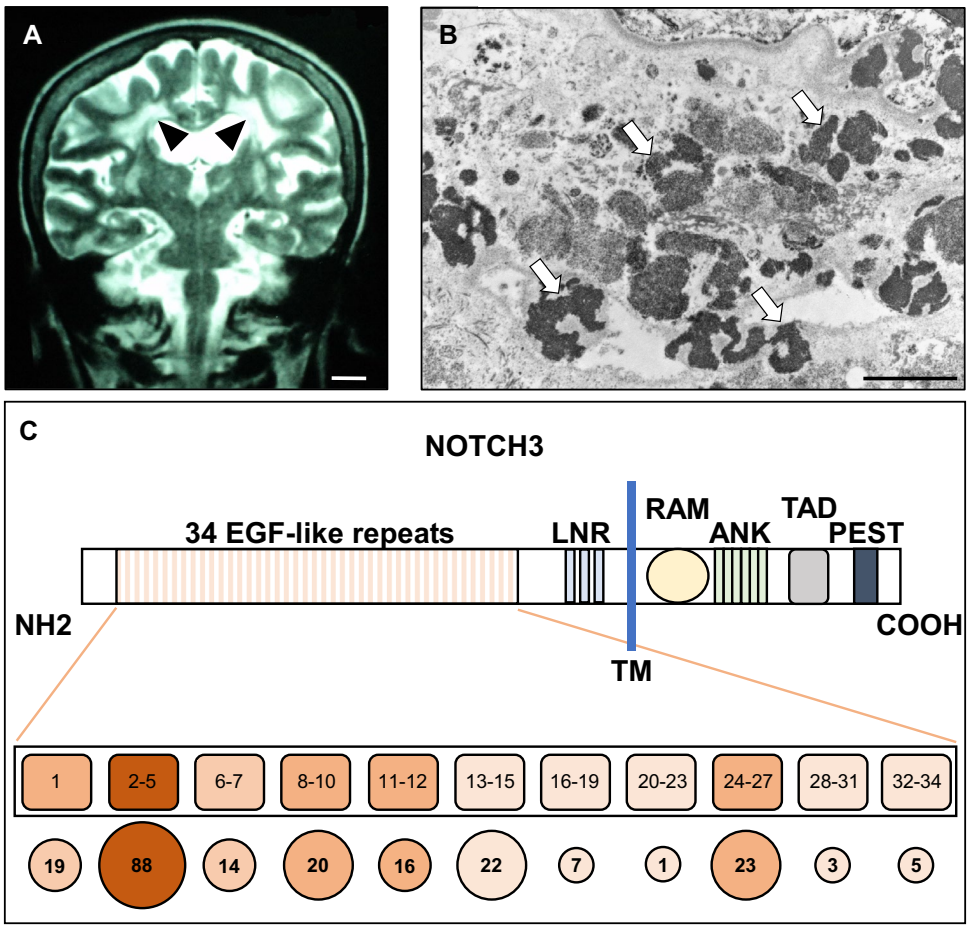

Fig. 3 CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). **a** Coronal MR imaging of a patient with the C455R mutation in NOTCH3 shows characteristic white matter lesions (arrowheads). Image courtesy of Dr. Francisco Lopera (University of Antioquia, Colombia). **b** Electron micrographs of subcortical white matter of postmortem brains from an individual carrying the C455R mutation shows abundant electron-dense granular osmiophilic (GOM) deposits (arrows). Scale bars: **a** 1.4 cm; **b** 2 µm. **c** Structure of the Notch3 receptor. A schematic of the receptor indicating key structural features. The 34 epidermal growth factor-like (EGF-like) repeats and the 3 Lin12-Notch repeats (LNR) are indicated in the extracellular domain. The transmembrane (TM), and the intracellular RAM, ankyrin repeat region (ANK), TAD, and PEST domains are also shown (top). Distribution of known CADASIL mutations along the EGF-like repeats (bottom). The relative size of circles below the schematic indicates the number of mutations reported for each cluster of EGF repeats

thickening of the arterial wall and prominent morphological alterations, and ultimately, loss of vascular smooth muscle cells and pericytes [192, 209–211]. A specific, and indeed pathognomonic, ultrastructural feature of CADASIL is the presence of granular osmiophilic material (a.k.a. GOM) (Fig. 3b) close to the cell surface of smooth muscle cells and pericytes in brain and skin arteries [210, 212–215]; these deposits are mostly extracellular and of variable morphology, size, shape, and osmiophilic density. Their detection by electron microscopy in skin biopsies represents a highly reliable diagnostic method [194, 214]. Extensive accumulation of the Notch3 extracellular domain has been reported in arterial walls, capillaries, and, possibly, GOMs [216–218]. Direct proteomic analysis of blood vessels from postmortem brains of CADASIL patients identified additional components of the GOM, including the proteins clusterin and collagen 18α1/endostatin, as well as various proteins of the extracellular matrix [219]. Further proteomic and immunohistochemical analyses identified two functionally important ECM proteins, tissue inhibitor of metalloproteinases 3 (TIMP3) and vitronectin, which are sequestered in aggregates containing the extracellular domain of Notch3 [218]. The latent TGF-β binding protein 1 (LTBP-1) is also thought to be recruited to these aggregates [220]. Finally, enrichment in brain collagen subtypes has also been reported in the arterial vessel wall of CADASIL patients [142]. The functional, structural, and cell biological consequences of extracellular Notch3 receptor CADASIL-linked mutations remain incompletely understood (for a discussion, see [194, 221]).

An extraordinary feature of CADASIL is the commonality of the disease-causing mutations in the Notch3 receptor (Fig. 3c). They are highly stereotypical, affecting exclusively the extracellular domain and occur in exons 2–24, encoding the EGF-like repeats, with a strong clustering in exons 3 and 4 [222]. More than 95% of the mutations are missense, whereas the remaining are small in-frame deletions or splice site mutations. Importantly, the vast majority of mutations lead to an odd number of cysteine residues within the affected EGF-like repeat; rare cysteine-sparing mutations have been reported in patients with clinical picture considered to be compatible with CADASIL (e.g., [223, 224]). However, the causal relationship between disease and these variants remains a matter of debate [194]. Perhaps surprisingly, given that the mutations were identified more than 20 years ago, the jury is still out, despite considerable effort from many groups using in vitro assays, as well as analyses in model organisms [219, 225–230]. Attaining a molecular understanding of CADASIL pathophysiology is essential if we are to contemplate a rational therapeutic approach to this devastating disease. In particular, determining the nature of the CADASIL-linked mutations is essential as gain or loss of function abnormalities would be treated radically differently. The extraordinary pleiotropy of Notch, including a profound involvement in the biology of adult stem cells, presents also a great challenge, as modulating its activity for therapeutic purposes will be highly dependent on the cellular context and quantitative aspects of signal modulation, carrying thus implicitly the danger of unacceptable toxicities.

CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy)

CARASIL is an ischemic, non-hypertensive, very rare cerebral SVD, with the majority of the approximately 50 known cases reported in Japan [194, 231]. Clinical signs include a stepwise deterioration in brain functions and progressive dementia; the disease is characterized by diffuse white matter changes and multiple lacunar infarctions in the basal ganglia and thalamus. Histological findings include intense atherosclerosis affecting mainly small penetrating arteries; GOM or amyloid deposits are however absent. Biallelic mutations in *HTRA1*, encoding a serine protease implicated in negative regulation of TGFβ signaling, have been associated with CARASIL [183, 232]; interestingly, heterozygous *HTRA1* mutations have also been reported in a family with autosomal-dominant SVD with clinical features distinct from CARASIL and CADASIL [233].

Cerebral amyloid angiopathy (CAA)

CAA, a common clinical entity in elderly patients, is characterized by accumulation of amyloid fibrils, cleavage products of the Amyloid Precursor Protein (APP), within the wall of small- to medium-sized vessels of the brain and leptomeninges [186, 187]. CAA is a major cause of primary intracerebral hemorrhage leading in most cases to cognitive decline, dementia, or death [234–236]. Notably, these symptoms also characterize Alzheimer's disease (AD), often confounding diagnosis. AD and CAA can be thought as related diseases with overlapping pathogenesis. It is indeed true that most patients with AD have some degree of CAA [237, 238]; however, the clinical features of CAA and AD differ. CAA, being a vascular disorder, is mainly characterized by small intracranial hemorrhages leading to stepwise cognitive decline. AD presents with progressive cognitive decline leading to terminal dementia [239, 240]. Amyloid beta (Aβ) aggregates accumulate in the parenchyma in the form of neuritic plaques in AD pathology, whereas in CAA they form in the walls of small arteries and arterioles.

CAA and its clinical complications are typically prevalent in the elderly: while postmortem series revealed at least moderate CAA in 2.3% of autopsies performed at age 65–74, about 12% of individuals older than 85 years harbored CAA [241], suggesting a significant age-dependent increase in disease prevalence. Overall, most of Aβ-CAA cases are sporadic, although genetic risk factors exist. Of interest, genetic variants implicated in AD, e.g., apolipoprotein E, presenilin 1, α-1 antichymotrypsin, and neprilysin, are also associated with increased risk for CAA [242]. As in AD [243], a high frequency of the ApoE ε4 allele correlates with the severity of CAA [244]. Consequently, CAA and AD do not only share a similar fingerprint regarding their characteristic clinical symptoms, but also similar genetic underpinnings.

In addition to sporadic cases, numerous hereditary forms of CAA have been reported. The pedigrees of the affected families reveal frequently an autosomal-dominant pattern of inheritance, involving *APP* on chromosome 21 [245]. Mutations mapping close to the cleavage sites of APP result in early-onset AD, whereas those affecting residues 21-23 and 34 of the Aβ peptide are associated with a broad spectrum of CNS diseases, including CAA [246]. Hereditary CAAs are sub-categorized according to their geographical area of prevalence, e.g., the Italian (E693K), Flemish (A692G), and Arctic (E693G) variants [236]. Neuropathological outcomes extend from increased Aβ production to abundant neurofibrillar appearance, with all eventually resulting in Aβ deposits [247, 248]. Although more rarely, CAA can also be characterized (and neuropathologically verified) by depositions of cystatin C (HCHWA-I), diverse transthyretins, or gesolin fragments, which are all associated with mutations in the genes encoding the respective proteins [249–251]. Non-Aβ phenotypes are also most often inherited in an autosomal-dominant pattern. Protein accumulations within the vessel wall represent only the first step in CAA pathogenesis, and are often accompanied by loss of smooth muscle cells,

obliterative intimal changes, as well as microaneurysmal dilatations [236]. Animal models for CAA [252, 253] have yet to provide significant insight into the exact mechanisms leading to these structural changes.

Cerebroretinal vasculopathies (CRVs)

CRVs are a collection of severe autosomal-dominant disorders with middle-age onset and 100% penetrance presenting with vasculopathy that predominantly involves the white matter and the retina [188], caused by C-terminal truncating mutations in *TREX1*, which encodes the 3' to 5′ exonuclease DNAse III [184]. The truncating mutations do not interfere with enzymatic activity, but disrupt subcellular localization; however, the mechanism(s) by which these mutations lead to microvascular endotheliopathy remain unknown [254].

Conclusion

Many cerebrovascular disorders are associated with genetic lesions; for some, such as CADASIL, a clear monogenic link has been established, while for others, an interplay of genetic susceptibility with environmental and other risk factors contributes to pathogenetic mechanisms leading to disruptions of the cerebral vasculature. Gene discovery in cerebrovascular disease, made possible by advances in genetics and genomics, not only refines our understanding of the basic biological mechanisms governing the development and homeostasis of the neurovascular unit, but has the potential to inform strategies for the development of rational therapeutic approaches. Expanding our understanding of pathophysiology in the context of familial forms, should also help elucidate the mechanisms underlying sporadic forms of disease.

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