Shared associations of nonatherosclerotic, large-vessel, cerebrovascular arteriopathies: considering intracranial aneurysms, cervical artery dissection, moyamoya disease and fibromuscular dysplasia

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Purpose of review
With ongoing advancements in noninvasive vascular imaging and high-throughput genomics, we have the opportunity to reclassify the cerebrocervical disorders by these shared associations, rather than their downstream events, and to better understand etiology, mechanism and preventive treatments going forward.

Recent findings
The common nonatherosclerotic, large-vessel arteriopathies affecting the cerebrovasculature include intracranial aneurysms, cervical artery dissection, fibromuscular dysplasia and moyamoya disease. Together, these entities contribute to a high incidence of devastating cerebrovascular outcomes, including ischemic stroke and subarachnoid hemorrhage, leading to long-term physical and cognitive disability frequently in young otherwise healthy adults. In addition to well reported clinical overlap, these polygenic phenotypes share epidemiological characteristics, environmental risk and a common pathological weakening of the arterial wall.

Summary
We reviewed both past and present studies relating these shared associations, including reported candidate gene analyses and genome-wide association data. We also catalogue recent descriptions of novel arteriopathic syndromes that add to the growing list of monogenic connective tissue disease affecting the arterial wall, and further inform our understanding of more common polygenic phenotypes. We also place these cerebrocervical arteriopathies in the context of other systemic nonatherosclerotic, large-vessel vascular disease (e.g. aortic aneurysm and dissection).

Keywords
aneurysm, arteriopathy, artery dissection, fibromuscular dysplasia, genetic, moyamoya

INTRODUCTION

Cerebrovascular disease has long been categorized by clinicoanatomic characteristics: ischemic vs. hemorrhagic, thrombotic vs. embolic, and so on. Rapid advancements in noninvasive vascular imaging and high throughput genomics create the opportunity to reclassify neurovascular disorders by considering them in the context of shared associations. This strategy allowed reconceptualizing small vessel disease through a shared pathogenesis encompassing lacunar stroke, hypertensive hemorrhage, leukoariosis and deep cerebral microbleeds [1,2▪,3].

Common nonatherosclerotic, large-vessel cerebrocervical arteriopathies include intracranial aneurysms, cervical artery dissection (CeAD), moyamoya disease and fibromuscular dysplasia (FMD). Current clinical classification systems (WHO) [4], TOAST [5], Causative Classification System [6]) frequently lump these as minority causes of stroke [7].

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KEY POINTS

- Among arteriopathic connective tissue disorders, monogenic and polygenic phenotypes share common clinical, pathological and genetic associations.
- The common nonatherosclerotic, large-vessel, cerebrocervical arteriopathies include intracranial aneurysms, cervical artery dissection (CeAD), moyamoya disease and fibromuscular dysplasia (FMD), collectively responsible for a large number of incident strokes among young and healthy adults.
- These arteriopathies share pathogenesis stemming from loss of structural integrity in the arterial wall; specific alterations include functional transformation of smooth muscle cells (SMCs), degradation of the elastic laminae, functional changes in collagen deposition and inflammation.
- Appreciating shared associations among these arteriopathies will guide future etiological research and hopefully inform potential therapeutic targets to prevent downstream cerebrovascular events in the future.

We reconsider these large-vessel cerebrocervical arteriopathies on the basis of shared clinical characteristics, pathogenesis and genetic risk, dichotomizing between monogenic and polygenic phenotypes.

MONOGENIC ARTERIOPATHIC CONNECTIVE TISSUE DISORDERS

Of the structural elements of the arterial wall, comprising intima, media and adventitia, tensile strength relies primarily on smooth muscle cell (SMC) integrity and collagen type III (COL3A1), the principal component of the extracellular matrix (ECM) and the defective gene product in vascular Ehlers-Danlos IV (vEDS) [8]. Additional key components of the ECM include the elastic lamina, fibroblasts, proteoglycans and fibrillin, defective in Marfan syndrome [9]. Ultrastructure of the arterial wall demonstrates numerous potential targets for congenital weakening (Fig. 1) [10].

These well described and other more recently defined monogenic connective tissue disorders predispose to arteriopathy (Table 1) [11–13,14▪,15▪,16–28,29▪,30–36,37▪,38,39,40▪,41–44,45▪,46,47].

Prevalence ranges broadly from one in 400 for autosomal dominant polycystic kidney disease (ADPKD) [48,49] to disorders described in single families. Connective tissue disorders such as Loeys–Dietz [50] and 'multisystemic smooth muscle dysfunction syndrome' [43] that predispose to arteriopathy continue to be described.

Common (polygenic) large-vessel arteriopathies

The relationship between monogenic connective tissue disease and polygenic phenotypes is unclear. For example, only 1–2% of intracranial aneurysm or CeAD cases prove to be syndromic [51–53], with the majority being spontaneous or idiopathic not manifesting overt signs of collagen vascular disease. This discrepancy likely stems from low penetrance variants and additional nongenetic factors discussed here.

Intracranial aneurysms

Saccular intracranial aneurysms represent the most prevalent cerebral large-vessel, nonatherosclerotic arteriopathy with rupture leading to subarachnoid hemorrhage (SAH), associated with high mortality and morbidity. Most commonly occurring at bifurcations with a predilection for the anterior circulation, biomechanical weakening in the arterial

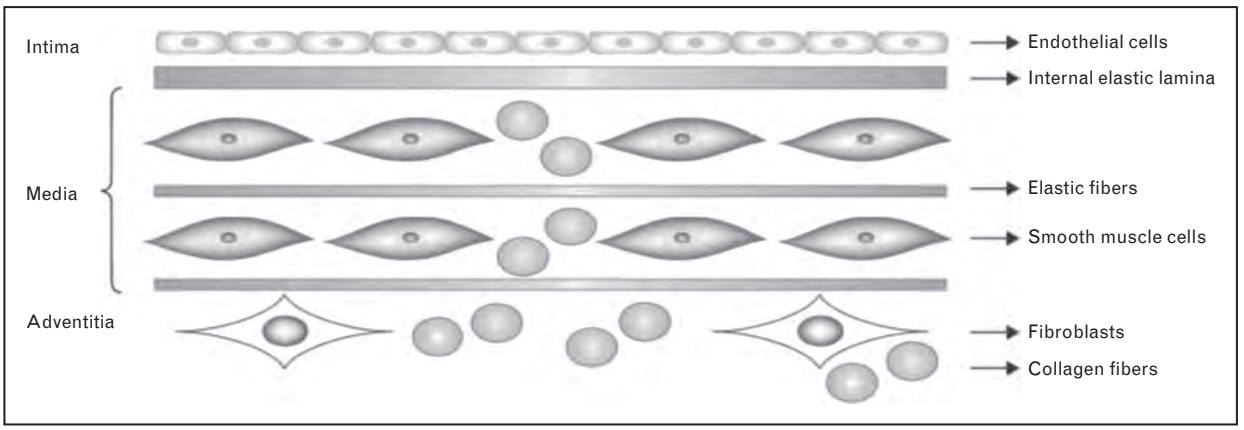

FIGURE 1. Ultrastructure of the arterial wall. Representative of an intracranial artery; extracranial arteries also have an external elastic lamina between the media–adventitia. Reprinted with permission from [10].

Table 1. Monogenic syndromes with overlapping cerebrocervical and extra-cerebral arteriopathies

Name (abbreviation; OMIM listing)	Gene/locus	Inheritance	Cerebrocervical arteriopathy	Extra-cerebral arteriopathy	Other features
Vascular Ehlers-Danlos type IV (vEDS; OMIM 130050)	*COL3A1*	AD	IA, CeAD	TAA, AAA, aortic dissection	Joint and dermal manifestations, prone to spontaneous rupture of bowel and large arteries
Marfan syndrome (MFS; OMIM 154700)	Fibrillin-1 (*FBN1*)	AD	IA, CeAD [11]	TAA, AAA, aortic dissection	Hallmark skeletal, ocular and cardiovascular features. Arachnodactyly and subluxation of the lenses
Arterial tortuosity syndrome (ATS; OMIM 208050)	*SLC2A10* [12]	AR	IA, CeAD	TAA, AAA	Generalized tortuosity and elongation of all major arteries, soft skin, joint laxity, severe keratoconus
Adult polycystic kidney disease (PKD1; OMIM 173900)	*PKD1*	AD	IA, CeAD	TAA, AAA, aortic dissection	Renal cysts, liver cysts
Adult polycystic kidney disease (PKD3; OMIM 600666)	Unknown [13]	AD	IA	Unknown	Renal cysts, liver cysts
Loeys-Dietz syndrome type 1A (LDS1A; OMIM 608967)	*TGFBR1*	AD	A, CeAD	TAA, AAA, aortic dissection, other vessel dissection	Triad of arterial tortuosity and aneurysms, hypertelorism, bifid uvula/cleft palate; pregnancy complications
Loeys-Dietz syndrome type 1B (LDS1B; OMIM 610168)	*TGFBR2*	AD	IA, CeAD	TAA, AAA, aortic dissection,other vessel dissection	Indistinguishable from LDS1A
Loeys-Dietz syndrome type 2A (LDS2A; OMIM 610380)	*TGFBR1*	AD	IA, CeAD	TAA, AAA, aortic dissection,other vessel dissection	Phenotypically similar to vEDS, bifid uvula is usually only craniofacial feature
Loeys-Dietz syndrome type 2B (LDS2B; OMIM 610380)	*TGFBR2*	AD	IA, CeAD	TAA, AAA, aortic dissection, other vessel dissection	Indistinguishable from LDS2A
Loeys-Dietz syndrome type 3 (LDS3; OMIM 613795)	*SMAD3*	AD	IA, CeAD	TAA, AAA, aortic dissection, other vessel dissection [14▪]	Previously known as aneurysm–osteoarthritis syndrome [15▪]; congenital heart disease
Loeys-Dietz syndrome type 4 (LDS4; OMIM 614816)	*TGFB2*	AD	IA, CeAD	TAA, AAA	Skeletal manifestations, bicuspid aortic valve, arterial tortuosity, arachnodactyly, scoliosis, club feet and thin skin with easy bruising and striae
Osteogenesis imperfecta type 1 (OI1; OMIM 166200)	*COL1A1*	AD	CeAD, FMD [16]	TAA, AAA	Multiple bone fractures, hearing loss, blue sclera
Alpha-1 antitrypsin deficiency (OMIM 613490)	*SERPINA1*	AR	FMD [17–21]	None	Emphysema, liver disease
Psuedoxanthomaelasticum (PXE; OMIM 264800)	ATP-binding cassette subfamily C member 6 (*ABCC6*) [22]; polymorphisms in xylosyl transferase gene, *XYLT1* (608124) and *XYLT2* (608125) modify severity of PXE [22]	AR, pseudo-dominant	IA, [23]; CeAD [24]	?AAA [25]	Mineralized and fragmented elastic fibers in the skin, vascular walls and Burch membrane in the eye
Microcephalic osteodysplastic primordial dwarfism type II (MOPD2; OMIM 210720)	*PCNT*, pericentrin, 21q22 [26]	AR or compound heterozygous	IA, moyamoya	TAA, AAA	Postnatal dwarfism with microcephaly and dysmorphia
Neuro-fibromatosis type 1 (NF1; OMIM 162200)	Neurofibromin gene (*NF1*); 17q11.2 [27]	AD	IA, moyamoya	Coartaction of thoracic and abdominal aorta, venous and arterial aneurysms	Aortic aneurysms, moyamoya [28]
Grange syndrome (OMIM 602531); arterial occlusive disease, progressive, with hypertension, heart defects, bone fragility, and brachysyndactyly	Unknown; unknown [16,29▪,30]	Unclear	IA, moyamoya	TAA, AAA, venous and arterial aneurysms	Stenosis or occlusion renal, abdominal and cerebral arteries. Cerebral aneurysms, congenital heart defects, brachydactyly, syndactyly, bone fragility and learning disabilities

Table 1 (*Continued*)

Name (abbreviation; OMIM listing)	Gene/locus	Inheritance	Cerebrocervical arteriopathy	Extra-cerebral arteriopathy	Other features
Hereditary angiopathy with nephropathy, aneurysms and muscle cramps (HANAC; OMIM611773)	*COL4A1*	AD	IA [31–34]	TAA, AAA, arterial aneurysms	Associated with a small vessel arteriopathy [35,36] and risk of ICH [37▪]
Alport syndrome X-linked (ATS; OMIM 301050)	*COL4A5*	AD	?CeAD, FMD and moyamoya [38]	TAA, AAA [39]	Progressive glomerulonephropathy, variable sensorineural hearing loss and variable ocular anomalies
SAMS (stenosis, aneurysm, moyamoya and stroke) [40▪]	*SAMHD1*	AR or compound heterozygous	IA, moyamoya [41]	?aortic aneurysm	Cerebral vasculopathy and early onset stroke [40▪,41,42]; same gene mutated in chilblain lupus (CHBL2; 614415) and Aicardi-Goutieres syndrome (AGS5; 612952)
Homocyst(e)inuria (OMIM 236200)	*CBS*	AR	?CeAD	Aortic dissection	Marfanoid phenotype
Multisystemic smooth muscle dysfunction syndrome (OMIM 613834) a.k.a. moyamoya type 5 (MYMY5; OMIM 614042) and familial thoracic aortic aneurysm type 6 (AAT6; OMIM 611788)	*ACTA2*	AD	?IA, moyamoya	Aortic dissection, TAA, AAA [43,44,45▪,46]	Mydriasis, patent ductus arteriosus, hypotonic bladder, malrotation and hyperperistalsis of the gastrointestinal tract
Cutis Laxa type IA; (ARCL1A; OMIM 219100)	*FBLN5*	AR	IA, FMD [47]	TAA, AAA, aortic dissection	Phenotypically similar to vEDS; multiple diverticula (esophagus, duodenum, ileum, bladder). The other had pulmonary emphysema

OMIM, Online Mendelian Inheritance in Man database (www.ncbi.nlm.nih.gov/omim). AAA, abdominal aortic aneurysm; AD, autosomal dominant; AR, autosomal recessive; CeAD, cervical artery dissection; FMD, fibromuscular dysplasia; IA, intracranial aneurysm; ICH, intracerebral hemorrhage; TAA, thoracic aortic aneurysm.

wall leads to outpouching of all three arterial layers. A variety of ultrastructural defects are associated with aneurysms, including alteration in the elastin-to-collagen ratio, SMC transformation and migration to the intima, and protein dysfunction in the ECM. Yet, the hallmark pathological feature of intracranial aneurysm is degradation of the internal elastic lamina [10,54].

The prevalence of intracranial aneurysm (0.5–5% in autopsy series) and incidence of aneurysmal SAH (8–11/100 000 totalling approximately 30 000 cases per year in the USA) varies by region and population [10,55–60]. An international review of unruptured aneurysms found an overall prevalence of 3.2% [95% confidence interval (CI) 1.9–5.2], with no difference in prevalence ratios between countries, despite wide variance in SAH risk [61▪].

Nonmodifiable risk factors potentially affecting the risk of aneurysm growth and rupture include age, sex, race/ethnicity and genomics. Aneurysm rupture most commonly occurs between 40 and 60 years, peaking in the sixth decade [55,57]. Incidence of SAH is higher in women overall (1.6 : 1), but roughly equal in patients younger than 50 years [10,57,60,62]. Sex differences may reflect hormonal interactions with vascular wall integrity. A recent meta-analysis confirmed an increased risk for SAH among postmenopausal women compared with premenopausal women of the same age, but failed to show a significant relationship between hormone replacement therapy and SAH [63,64▪].

Risk for intracranial aneurysm rupture also differs by race and ethnicity. Several community-based US cohorts demonstrate higher incidences of SAH in African-Americans and Hispanics than non-Hispanic whites [58,62,65,66]. Globally, Finland and Japan have the highest incidence of SAH [67–69]. Whether genetics or environmental risk explains these differences remains unresolved.

Data regarding aneurysm size and risk for rupture conflict. The International Study of Unruptured IAs (ISUIA) reported an overall low risk of SAH for small (<10 mm) unruptured aneurysms [70,71], yet the majority of ruptured aneurysms are less than 10 mm [72]. Aneurysms may experience a peak period for growth and rupture risk related to

hemodynamics, vascular wall integrity and environmental risk factors, especially smoking [73–75,76▪], accounting for variance in SAH risk among aneurysms of the same size and across populations with the same intracranial aneurysm prevalence. The high early rerupture risk (50% by 6 months) contrasting with low rates of long-term recurrence (3% annually) further supports the notion of peak vulnerability [77–79].

Familial clustering of intracranial aneurysm and SAH is found in 10–15% [80], likely an underestimate due to ascertainment bias [81]. Nevertheless, those with two or more affected family members have a four-fold risk of harbouring an intracranial aneurysm compared with the general population [48,53]. Case–control analyses and linkage studies identified several candidate genes for intracranial aneurysm [10]. A large genome-wide association study (GWAS) of intracranial aneurysm in European and Japanese populations revealed significant associations with sequence variants in chromosome 8q11 and 9p21 [82], which were replicated in 406 familial cases from the Familial Intracranial Aneurysm (FIA) Study [83]. Further data from FIA support the association of these two regions in familial and sporadic disease [84▪▪] and reinforce a strong interaction with smoking, the greatest modifiable risk factor for aneurysmal rupture [83]. Table 2 summarizes currently associated variants for intracranial aneurysm risk [82,83,84▪▪,85–88].

Cervical artery dissection

Cervical artery dissection – dissection of the carotid or vertebral arteries – accounts for approximately 20% of ischemic stroke in adults aged 18–50 years [89,90]. Annual incidence of CeAD is reported as 2–4/100 000, likely an underestimate due to diagnostic bias [91,92].

Most CeAD occurs spontaneously, although minor neck trauma or exertion, ranging from coughing to riding a roller coaster, is frequently associated [93▪,94]. Shear forces are likely only an environmental trigger in genetically or physiologically predisposed individuals [95▪]. Maximum wall stress on the cervical arteries occurs with 90° lateral rotation or 45° rotation with hyperextension [96▪]. Carotid dissections typically occur at a susceptible segment several centimeters distal to the bifurcation, anchored by the trunk proximally and petrous bone distally [96▪]. Vertebral dissections typically involve the vulnerable V2/V3 junction where the artery exits the C2 transverse foramen and enters the dura [97]. Additional physiological or environmental associations include hypertension, low cholesterol, increased height with low weight, infection or systemic inflammation, migraine, peripartum and a seasonal variation with fall and winter peaks [89,98▪,99▪,100–102].

CeAD mostly occurs between 30 and 50 years of age, with median age 5–10 years younger in women than men [98▪,103,104]. A transient peak

Table 2. Genome-wide associations for intracranial aneurysms

Locus	Nearest gene	Study	Cohort	Putative function	Associations (OMIM)
11q24–25	*FAA1*	Ozturk *et al.* [85], Worrall *et al.* (linkage) [86]	Familial (European)	Fatty acid metabolism	TAA, AAA
9p21	*CDKN2BAS/ANRI*	Bilguvar *et al.* [82], Deka *et al.* [83], Yasuno *et al.* [87], Foroud *et al.* [84▪▪]	Familial + sporadic (European, Japanese)	Noncoding RNA, P15 (INK4b), P16 (INK4a)	CAD, AAA, LAA, DMII
8q11-12	*SOX17*	Bilguvar *et al.* [82], Deka *et al.* [83], Yasuno *et al.* [87], Foroud *et al.* [84▪▪]	Familial + sporadic (European, Japanese)	Endothelial cell metabolism	Congenital kidney and urinary tract anomalies
2q33	*PLCL1*	Bilguvar *et al.* [82]	European (Finnish, Dutch) Japanese	VEGFR2 signalling	
10q24	*CNNM2*	Yasuno *et al.* [87]	European (Finnish, Dutch, German) Japanese	Cyclin M2	CAD, HTN, renal tubular malabsorption of magnesium
13q13	*STARD13, KL* (klotho)	Yasuno *et al.* [87]	European (Finnish, Dutch, German) Japanese	FGF receptor specificity, accelerated ageing	Carcinomas, CKD, hypocalcinosis
18q11	*RBBP8*	Yasuno *et al.* [87]	European (Finnish, Dutch, German) Japanese	Retinoblastoma binding protein, DNA repair	Tumourigenesis
4q31	*EDNRA*	Yasuno *et al.* [88]	Finnish, Japanese	Endothelin receptor	HTN, CHF, migraine

OMIM, Online Mendelian Inheritance in Man database (www.ncbi.nlm.nih.gov/omim). AAA, abdominal aortic aneurysm; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; DMII, type II diabetes mellitus; HTN, hypertension; TAA, thoracic aortic aneurysm.

in vulnerability seems likely, given high short-term recurrence rates of stroke or dissection (~25%), and low long-term recurrence of approximately 1–2% per year [105–107]. CeAD is uncommon in the very old, perhaps reflecting a protective stiffening of arteries over time [108]. Arterial dissections in children more commonly occur intracranially [109], whereas pure intracranial dissection in adults is rare [110].

Ultrastructural abnormalities reflecting inherent weakening of the arterial wall support a genetic cause for CeAD. Histologically, this includes medial degeneration, degradation of the external elastic lamina, neoangiogenesis of the vasavasorum and extravasation of blood in the medial–adventitial border. A generalized arteriopathy is supported by similar abnormalities in both dissected and clinically unaffected arteries [111,112,113▪] and that 15–20% of incident cases have multivessel dissections [105]. Although most CeAD cases display no other phenotypic signs [51,52], subtle indications of underlying connective tissue disease include heritable dermal collagen defects, keloid scarring, aortic root dilatation and redundant arterial looping or kinking [114,115–118]. Familial CeAD is rare, associated with younger age, more commonly polyarterial and more likely to recur [51,114,119].

Candidate gene analyses in CeAD have been underpowered and yield few significant or replicated results [120]. The most robust association is in the methylenetetrahydrofolate reductase (MTHFR) variant 677TT; a meta-analysis of five studies ($N = 440$ cases) revealed an increased risk for CeAD in those with the 677TT genotype with odds ratio equal to 1.67 (95% CI 1.21–2.31) [120]. Table 3 [120,121▪,122▪] presents reported candidate gene variants associated with cases of CeAD [1,12,120].

Replication has recently been completed in the largest GWAS of CeAD to date – an international multicenter consortium titled CADISP – Cervical Artery Dissection and Ischemic Stroke Patients [123]. With published results pending and an exome sequencing project underway, the CADISP study will shed better light on the genetic associations of CeAD.

Moyamoya disease

Moyamoya, another poorly understood arteriopathy [124▪], derives its name from the characteristic angiographic pattern [125]. The name means 'hazy puffs of smoke' describing the small vessel collateral system that develops in response to hyperplastic stenosis and occlusion of the distal internal carotid and proximal vessels of the circle of Willis. This process may be primary moyamoya disease, a progressive, often hereditary disorder, or moyamoya syndrome secondary to vasculopathies, including atherosclerosis, sickle cell disease and inherited thrombophilias. Although most patients with moyamoya disease are children, a second peak occurs between ages 25 and 50 years [126] with a slight female predominance [127]. Clinical presentations differ by age and include cerebral ischemia, intracerebral hemorrhage and cognitive impairment.

Moyamoya disease, most common in Asian countries and in those of Asian ancestry [128], affects 3–4 per million in Asian countries and less

Table 3. Gene variants in cervical arterial dissection

Gene (variant)	Locus	Product/function	Cohort	Additional associations
MTHFR (C677T)	1p36	Folate metabolism, amino acid synthesis	European (Italian, German), Mexican	Hyperhomocysteinemia, venous thrombosis
ICAM1 (469E)	19p13	Immune cell migration across vascular endothelium	European (German)	Inflammation, infarct size, SAH, aneurysm growth
COL3A1 (3'UTR)	2q31	Type III collagen, primary component of ECM and arterial tensility	European (German, Swiss) familial	Vascular Ehlers-Danlos IV, familial dermal connective tissue abnormalities
COL5A2 (D1429V)[a]	9q34	Type V collagen; fibrillar forming; low abundance in ECM	European (German)	Classical Ehlers-Danlos I/II
TGFBR2 (pK372R, pC138R)[b]	3p22	Regulates SMC migration and transformation, ECM metabolism	European (Italian)	Loeys-Dietz syndrome

ECM, extracellular matrix; SAH, subarachnoid hemorrhage; SCM, smooth muscle cell. Adapted from [120,121▪,122▪].
[a]Gene sequencing (1/60 cases); mutation not found in 150 healthy controls.
[b]Gene sequencing (2/56 cases); mutation not found in 500 healthy controls.

than 1 per million in the USA [128]. Founder mutations have been reported in Asian populations [129,130▪] and potential differences in genetic architecture may underlie moyamoya disease in those of Asian vs. European ancestry [131▪,132]. Most familial cases appear to be autosomal dominant with incomplete penetrance, although other modes are described, and genomic imprinting has been implicated [133].

Histologically, moyamoya disease shows characteristic proliferation of transformed SMCs and fibroblasts with thickening of the intima and concomitant thinning of the media. The intimal hyperplasia results in narrowing and ultimately obstruction of the vessel lumen leading to irregular collateral networks [134]. Ischemia results from compromised perfusion through stenosed large arteries and microthrombi in small vessels due to slow flow state and proinflammatory milieu [135]. Recurrent hypoxia and reduced blood flow stimulates angiogenic signals and growth factors that may play a role in aberrant collateralization [136▪]. These collateral vessels are friable with reduced structural integrity likely contributing to a higher risk of hemorrhage.

Five discrete genetic moyamoya disease syndromes (MYMY1–5) are currently characterized [27,43,46,133,137,138▪,139▪,140,141], and several additional syndromes manifest moyamoya changes as part of their phenotypic spectrum [16,26,27]. Moyamoya disease shares risk with other cerebral and systemic vasculopathies. Table 4 demonstrates multiple overlaps with systemic and cerebral aneurysms [16,26–28,29▪,30,130▪,137,139▪,141–144,145▪,146▪,147–150,151▪].

Others have described a link with FMD [38]. In contrast to FMD, which typically affects the media, moyamoya is typified by intimal thickening. Moyamoya disease shares some pathological features with FMD, CeAD and intracranial aneurysms primarily constituting transformation of SMCs and degraded elastic laminae. The frequency of moyamoya arterial changes is higher in patients with CeAD and intracranial aneurysms than the general population [90,126].

Fibromuscular dysplasia

Extracranial cervical FMD is second to the renal arteries in prevalence. FMD is characterized by nonatherosclerotic, alternating dilatation and constriction of the arterial wall, giving a banded appearance, and can involve any of the three layers; the medial type is most common accounting for 90% of cerebrocervical cases [152]. Defective fibroblastic transformation in SMCs leads to downstream degradation of the elastic laminae, abnormal collagen synthesis and segmental fibroplasia [153,154]. Overall prevalence of cervical FMD ranges from approximately 0.3 to 3.0% in consecutive angiographic series [152,154]. Most prevalent in women of European descent, FMD primarily affects young and middle-aged adults [155]. The largest FMD registry to date ($N = 447$) reveals a mean age of approximately 52 years, older than previously reported [156▪]. A second peak occurs in children and adolescents, but is more commonly of the intimal type, with a greater predilection for the intracranial circulation, similar to CeAD [157].

Incidental diagnosis of cerebrocervical FMD has increased with availability of noninvasive vascular imaging, yet the risk of cerebrovascular events remains controversial. The relationship with aneurysms and dissection is clearer. In the US FMD registry, the coprevalence of dissection and aneurysms was 19.7 and 17%, respectively [156▪]. Of dissections, 75% involved the carotid, 21.6% renal and 17% vertebral arteries. Of aneurysms, most were observed in the renal and carotid arteries, which may also reflect pseudoaneurysms as sequelae of dissection. Intracranial (11.8%) and aortic (19.7%) aneurysms likely represented true aneurysms. Nearly 25% of those in the registry reported a family history of aneurysm [156▪]. With a lack of dedicated screening, prevalence of intracranial aneurysms in those with cerebrocervical FMD may range from 7.3 to 51% [158]. In a large series of spontaneous CeAD, FMD is found in 15–20% of cases [154,159,160] (Southerland, unpublished data). Although these series suggest a higher than expected coprevalence of FMD with dissections and aneurysms, diagnostic bias is likely and rates cannot be generalized to the asymptomatic FMD population.

Factors associated with FMD include smoking, exogenous estrogens, mechanical stress, family history of early cardiovascular disease and even human lymphocytic antigen type in a series of renal transplant patients [155,161]. The underlying cause of FMD is likely genetic, with incomplete penetrance of a possible autosomal dominant trait suggested by a number of pedigrees showing higher prevalence in first-degree relatives and identical twins [154,162–166]. The FMD registry reveals self-reported family history in 7.3%, somewhat lower than reported in prior series and likely an underestimate given the lack of routine family screening [156▪,162,166]. That FMD likely represents a heritable systemic arteriopathy is further supported by familial clustering of common carotid wall abnormalities in cases of renal FMD compared with matched controls [167,168].

Table 4. Genetics of moyamoya disease

Name	Gene, locus	Gene function	Mode	Associated features
MYMY1	3p26–p24.2 [137,142]	Matrix metalloproteinase	AD	
MYMY2	*RNF213*; 17q25.3 [27,130▪,139▪,143,144]	Ubiquitin ligase activity and ATPase activity	AD	Associated with HTN [145▪] and important role in vascular function [146▪]
MYMY3	Unknown; 8q23 [141]	Unknown – TIEG, transforming growth factor-beta-inducible early growth response	AD	
MYMY4	*BRCC3*; Xq28 [138▪,147]	Deubiquitinating enzyme	X-linked recessive	Short stature, hypergonadotropic hypogonadism and facial dysmorphism, dilated cardiomyopathy, premature graying of the hair and early-onset cataracts
MYMY5	*ACTA2*; 10q23.31 [43,46]	Mutations promote increased SMC proliferation, lead a hyperplastic 'vasculo-myopathy' [44]	AD	TAA, fusiform cerebral aneurysms, premature CAD. Initially reported as hereditary thoracic aortic aneurysm 6 with dissection (AAT6) [43]
Moyamoya disease	HLA; 6q25 [148–150,151▪]	Molecular mimicry; HLA molecules acting as receptors for microbes and drugs; HLA genes as markers linked with disease-related non-HLA genes	Complex	Potential explanation for regional differences
Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	*PCNT* (pericentrin); 21q22 [26]	Involved in the initial establishment of organized microtubule arrays of the centrosome	AR or compound heterozygous	Cerebral aneurysms, moyamoya
Neurofibromatosis type 1	*NF1* (neurofibromin) 17q11.2 [27]	Tumor suppressor, regulator of neurotrophin-mediated signalling	AD	Cerebral aneurysms, aortic aneurysms, moyamoya [28]
Grange syndrome	Unknown; unknown [16,29▪,30]	Unknown	AR	Stenosis or occlusion of multiple arteries, including renal, abdominal and cerebral arteries. Cerebral aneurysms, congenital heart defects, brachydactyly, syndactyly, bone fragility and learning disabilities

OMIM, Online Mendelian Inheritance in Man database (www.ncbi.nlm.nih.gov/omim). AD, autosomal dominant; AR, autosomal recessive; CAD, coronary artery disease; HLA, human leukocyte antigen; HTN, hypertension; SMC, smooth muscle cell; TAA, thoracic aortic aneurysm. Derived from OMIM.

Genomic association studies in FMD are lacking. A systematic screen of 35 patients with FMD for connective tissue genetic variants identified only two cases with a similar phenotype that had novel variants in the transforming growth factor β receptor1 gene warranting further investigation [169▪]. Table 5 presents these analyses and other case-reported syndromic associations [11,17–21,163,169▪,170–175].

The US FMD registry [176] and the ARCADIA/PROFILE (Assessment of Renal and Cervical Artery DysplasIA Register et PROgression of FIbromuscular Lesions) [177] biorepositories are in preparation for more formal candidate gene and genomic association studies.

Shared associations among polygenic phenotypes

The best argument that large-vessel cervicocerebral arteriopathies, including aneurysms, dissection, moyamoya and FMD, have common roots is through observed associations with one another.

Epidemiology

Schievink, Mokri, and colleagues suggested a unifying arteriopathy in a 1991 report of three families with CeAD and intracranial aneurysm in siblings, and later confirmed a higher prevalence of intracranial aneurysm among nonfamilial CeAD as well [7,178]. As stated, both dissections and aneurysms are associated with FMD at higher frequencies than the general population, as are intracranial aneurysms in moyamoya disease [126]. A true coprevalence between CeAD and FMD with moyamoya disease has only been reported in isolated cases and is difficult to distinguish from moyamoya syndrome resulting from distal carotid stenosis secondary to these entities [117,168–170]. Genetic syndromes with coprevalence of arteriopathies in the cerebral and extra-cerebral circulation exist

Table 5. Genetic investigations and syndromic reports of fibromuscular dysplasia

Gene/syndrome	Renal	Cerebrocervical
ACE	Insertion allele associated [170]	n/a
AT1R	No association [170]	n/a
AGT	No association [170]	n/a
Elastin	No association [163]	n/a
Alpha-1-antitripsin	No association [171]; Case report [20]	Case reports [17–19,21]
ACTA2	No association [172]	n/a
TGFBR1	n/a	No association [169▪]
TGFBR2	n/a	No association [169▪]
collagen 3A1	n/a	No association [169▪]
smooth muscle α-actin 2	n/a	No association [169▪]
SMAD3	n/a	No association [169▪]
Fibrillin (Marfan syndrome)	n/a	No association [169▪]; Case report [11]
Down syndrome	Case report [173]	n/a
Turner syndrome	n/a	Case report [174]
Neurofibromatosis I	Case report [175]	n/a

n/a, not available.

(Table 1). These clinical and genetic observations suggest more than a coincidental, common pathogenesis.

Age

As mentioned, aneurysmal SAH, spontaneous CeAD and symptomatic FMD all predominate in adults primarily ranging from 30 to 50 years, with a separate peak for adult cases of moyamoya. The reasons for this midlife peak are unclear, especially as each entity occurs to some degree at all ages. Natural vascular stiffening or accumulating atherosclerosis may explain the lower prevalence among the elderly. That some traditional age-related vascular risk factors are inversely associated with arterial dissection and aneurysm rupture further supports this idea. For instance, natural lipid deposition in the vessel wall may fortify a congenitally weakened artery protecting it from downstream events such as hemorrhage or dissection.

If these arteriopathies are genetically predisposed, the reasons why spontaneous CeAD and aneurysmal SAH are not more prevalent in adolescents and young adults are unclear. The separate age peaks for children and adults in moyamoya disease, FMD and dissection highlight a potential pathological variance between children and adults exemplified by the predominance of intimal FMD and intracranial dissection in children, as opposed to more medial FMD and extracranial dissection in adults. Intracranial aneurysms are rarely reported in children without other phenotypic connective tissue disease; possible reasons include an underdiagnosis due to a low risk of rupture or more likely an age-dependent component to aneurysm formation. Better understanding of how the cerebrovascular system ages both morphometrically and functionally may help unravel the pathogenesis of these polygenic phenotypes.

Sex

FMD, moyamoya and aneurysmal rupture are all more prevalent in women. Although CeAD occurs at roughly equal frequency by sex, women are consistently younger than men at age of occurrence, have more vertebral artery involvement and more commonly present with multiple artery dissections [98▪]. Dissection and risk of aneurysm rupture are more common in the peripartum period, perhaps related to hormonal shifts or an ever-changing physiological state [103,179,180]. Limited data suggest at least some relationship between exogenous estrogens and risk for intracranial aneurysm rupture, incidence of CeAD and symptomatic FMD [161,181,182].

The biological mechanism of a hormonal influence on risk for cerebrovascular events in these arteriopathies remains unknown. Women have stiffer arteries than men, particularly at younger ages, but both sexes see decreased arterial compliance with age [183,184]. Estrogen supplementation increases arterial compliance in postmenopausal women, as does free testosterone in older men [185,186]. Arterial compliance is increased in patients with CeAD compared with age-matched controls [187,188]. Arterial compliance in aneurysm growth is clearly increased, but relationships

between compliance and rupture may be more reliant on structural integrity at time-of-event.

Hormones may influence vessel wall physiology. In rat models of aortic aneurysm, men have decreased collagen deposition and increased levels of matrix metalloproteinases (MMPs), a key mediator of vascular remodelling, in aortic SMCs and ECM compared with females [189,190]. Estrogen may play a protective role by lowering MMP levels in the model [191]. MMP levels can be elevated in CeAD [192], but sex-stratified differences have not been studied.

Race/ethnicity

Incidence and clinical characteristics vary by phenotype across ancestral populations. Investigated cohorts of CeAD and FMD mostly comprise cases of European and Asian descent, with limited data for populations of African descent [123,193,194]. Dissection characteristics also differ by race/ethnicity; Asians have a higher predilection for intracranial dissection and posterior circulation involvement [195▪]. Intracranial aneurysms exhibit consistent prevalence throughout the world, but rupture rates vary widely. For instance, rates of aneurysmal SAH are highest in Japan and Finland despite no difference in prevalence of unruptured aneurysms compared with other countries [61▪]. In the United States, African-Americans and Hispanics have higher rates of aneurysmal SAH than non-Hispanic whites when controlling for additional risk factors [22,26,29▪,30]. Moyamoya disease, most prevalent in Asian populations, is reported worldwide with higher rates in those of African descent than those of European descent [196]. These population-based differences are vital to understanding the genetic heterogeneity. Future genomic association studies should strive to stratify with broad race/ethnic representation.

Disease

Disparate pathological processes underlie these large-vessel arteriopathies likely reflecting their polygenic origins; however, several unifying components stand out (Table 6) [10,54,95▪,111,112,113▪,115,152–154,192,197–206]. A functional transformation in SMCs of the arterial media is a common denominator for these phenotypes. Other processes, including degradation of the ECM and inflammation, may be downstream results from this unifying event. Structural patterns in the vessel wall are specific to different arterial beds, and alteration of this homeostasis in different phenotypes likely promotes arterial fragility and injury in the setting of otherwise normal physiological or environmental stress. Focus on shared disease among these arteriopathies should guide future association studies enlightening the search for therapeutic targets.

Environmental and physiological risk factors

Traditional vascular risk factors for atherosclerosis including hyperlipidemia, diabetes mellitus and high BMI show an inverse relationship with both arterial dissection and aneurysmal subarachnoid hemorrhage [99▪,181,182,207]. Although these associations may represent epiphenomenae, these chronic conditions may also provide inherent protective qualities. Lower cholesterol levels including treatment with lipid-lowering agents may increase risk for intracerebral hemorrhage [208–211]. Diabetes mellitus exhibits an inverse association with abdominal aneurysm formation as well, and is associated with increased collagen deposition, cross-linking and decreased degradation of the ECM in the arterial wall [212▪,213]. The inverse relationship with BMI may stem from a particular phenotypic profile for arteriopathic connective tissue disease, although most patients with spontaneously occurring cases do not exhibit a Marfan's phenotype [100].

Hypertension as a risk factor for these arteriopathies is challenging to understand [99▪,161,182], particularly given its high prevalence in the general population. The higher frequency of hypertension in FMD, CeAD, intracranial aneurysm rupture and moyamoya could reflect biomechanical effects on the arterial wall or secondary alterations in the autonomic or renin–angiotensin systems related to the vasculopathy itself. Although chronic hypertension is associated with abdominal aneurysms, the influence on formation of cerebral aneurysms is less clear. Further, arterial anomalies (kinking, redundancies and dilatations) typically seen in hypertension are observed in non-hypertensive patients with these nonatherosclerotic arteriopathies.

Smoking, ubiquitous in its adverse effects on the cerebrovascular system, also interacts with arterial wall integrity in arteriopathic connective tissue phenotypes. Dermal changes in chronic smokers demonstrate its effect on the elastic properties of connective tissue [214]. Smoking is a significant risk factor for aneurysmal SAH, particularly in women [182]. Smoking is more loosely associated with FMD [155,161]. No similar association with CeAD has been observed; in fact, smoking might have a potential protective effect provoking the possibility of a differential relationship between smoking and differing arteriopathic phenotypes [99▪,181].

Table 6. Common vessel wall disease for intracranial aneurysms, cervical artery dissection, moyamoya and fibromuscular dysplasia

Vessel wall component	IA [10,54]	CeAD [95▪,111,112,113▪, 115,192,197–200]	Moyamoya [201–205]	FMD [152–154,206]
SMCs	Migration of SMCs from media to the luminal surface in vascular wall remodelling	Medial degeneration with vacuolated SMCs, transformation from contractile to synthetic type; TGFB mutations in some	Myointimal thickening with migration and transformation of SMCs from contractile to synthetic type	Fibroblastic transformation of SMCs from contractile to synthetic
Elastic lamina	Degradation of the internal EL with aneurysm growth	Degradation of external EL at medial-adventitial border	Duplication and wavy appearance of the internal EL	Attenuation of elastic fibers in the media and laminae
Collagen and elastin	Decrease on collagen type III, elastin relative to other collagen types; fewer reticular fibers in medial layer	Heritable collagen and elastin abnormalities in skin biopsies;	Collagen:elastin ratio altered, long segments appear similar to bifurcations	Abnormal collagen synthesis from transformed SMCs
Inflammation	Constant turnover of proteins in ECM; increased proteases, macrophages in wall of both ruptured and unruptured IA	Temporal association with infection, inflammatory biomarkers; elevated serum MMP levels	MMP polymorphisms in association with moyamoya disease (MYM1)	Case reports of elevated MMP9, antiphospholipid antibodies

CeAD, cervical artery dissection; ECM, extracellular matrix; EL, elastic lamina; FMD, fibromuscular dysplasia; IA, intracranial aneurysm; MMP, matrix metalloproteinase; SMCs, smooth muscle cells.

Temporal patterns in environmental risk raise especially vexing questions. For instance, what additional factor causes pathologically weakened arteries to dissect at a predictable age with incidental trauma, perhaps simultaneously, with minimal lifetime risk of recurrence? What additional factor causes a small intracranial aneurysm to form, stabilize for many years, only to grow rapidly and then rupture? Why does incidentally found FMD remain asymptomatic, when other cases lead to stroke, dissection or aneurysm? Is unilateral moyamoya the same disease as bilateral moyamoya, the same disease in children as adults? The notion of transient periods of vascular vulnerability must be considered when investigating risk and indicates nongenetic factors at play. Associated risk periods may involve physiological vascular aging, comorbidities such as migraine, inflammatory processes or even a seasonal peak for cerebrovascular events [101,215,216▪,217]. Better understanding of environmental and physiological vulnerability is warranted.

Genetic

As noted in Table 1, there is a considerable genetic overlap between both the monogenic and polygenic large-vessel arteriopathies. In addition, extra-cerebral phenotypes involving primarily the aortorenal circulation share clinical, epidemiological, histological and genetic features with the cerebrocervical phenotypes discussed here. Although a detailed discussion of extra-cerebrocervical arteropathies is beyond the scope of this review, it is imperative that these entities be considered in pathogenetic classification and future studies of vascular connective tissue disease.

Recently completed, large, genomic association studies of both CeAD and intracranial aneurysm, and a planned association study in FMD, offer the potential to further elucidate genetic underpinnings of these polygenic phenotypes. Exome sequencing may reveal rare risk variants such as the recent characterization of *SMAD3* mutations in a family of thoracic/abdominal aortic aneurysms and intracranial aneurysms [14▪].

High throughput RNA expression analysis, proteomics and epigenomics should facilitate a more dynamic understanding of genetic function and pathogenesis. Gene expression analysis in patients with intracranial aneurysms, for instance, may elucidate the cellular processes in the arterial wall that lead to aneurysm growth and rupture [218,219]. Copy number variant analysis in moyamoya [220▪] and dissection [221▪] have started to yield results and will expand our understanding of genetic risk further.

CONCLUSION

In this review of the nonatherosclerotic, large-vessel cerebrocervical arteriopathies, we propose a unifying vessel wall pathogenesis affecting different segments of the arterial tree (Fig. 2). Refined understanding of shared associations, common biology and gene by environment interactions will hopefully lead to future scientific questions and ultimately better treatment strategies to prevent resultant cerebrovascular events in predisposed individuals going forward.

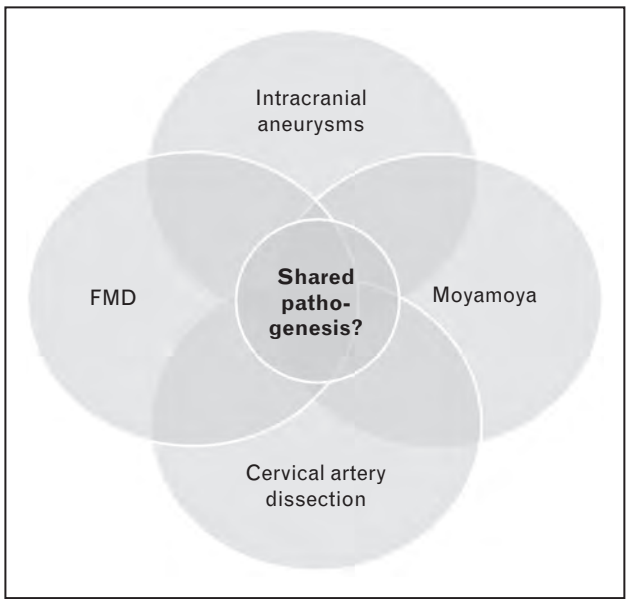

FIGURE 2. Overlapping relationship of polygenic cerebrocervical arteriopathies. Conceptual framework for shared mechanisms of nonatherosclerotic cerebrocervical large-vessel arteriopathy. FMD, fibromuscular dysplasia.

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Conflicts of interest

No commercial conflicts are reported by the authors. Dr Worrall serves as an Associate Editor for the Journal of Neurology.

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