**REVIEW ARTICLE** doi: 10.2176/nmc.ra.2016-0051

*Neurol Med Chir (Tokyo) 56, 317–325, 2016* Online April 14, 2016

# *Pathogenesis of Brain Arteriovenous Malformations*

Masaki KOMIYAMA[1]

[1]*Department of Neuro-Intervention, Osaka City General Hospital, Osaka, Osaka*

## Abstract

**Brain arteriovenous malformations (bAVMs) represent a high risk of intracranial hemorrhages, which are substantial causes of morbidity and mortality of bAVMs, especially in children and young adults. Although a variety of factors leading to hemorrhages of bAVMs are investigated extensively, their pathogenesis is still not well elucidated. The author has reviewed the updated data of genetic aspects of bAVMs, especially focusing on clinical and experimental knowledge from hereditary hemorrhagic telangiectasia, which is the representative genetic disease presenting with bAVMs caused by loss-of-function in one of the two genes: *endoglin* and *activin receptor-like kinase 1*. This knowledge may allow us to infer the pathogensis of sporadic bAVMs and in the development of new medical therapies for them.**

Key words: animal model, brain arteriovenous malformation, gene mutation, hereditary hemorrhagic telangiectasia, pathogenesis

## Introduction

Brain arteriovenous malformations (bAVMs) consist of abnormal tangles of dilated vascular structure called nidus, which connects arteries and veins directly without intervening capillary beds. They are one of the major causes of intracranial hemorrhage and/or subarachnoid hemorrhage, which lead substantial morbidity and mortality of bAVMs, especially in children and young adults. Primary rationale for treatment of bAVMs is to prevent new or recurrent hemorrhage. Current treatment modalities include surgical removal, endovascular treatment, and stereotactic radiosurgery.[1)] However, it is a current controversy that risks of these interventions for unruptured bAVMs may exceed that of best medical management.[2)] There is no medical treatment available to prevent development or rupture of bAVMs. Although pathogenesis of bAVMs is not yet well elucidated, genetic mutations and genetic risk factors are increasingly identified. Appropriate animal models of bAVMs are prerequisite for understanding of the pathogenesis and development of new therapies. The author reviewed pathogenesis of bAVMs using the current updated data, especially the new knowledge from clinical cases and animal experimental models of hereditary hemorrhagic telangiectasia (HHT), which is also known as Osler-Weber-Rendu disease.[3–5)] Since it is conceivable that bAVMs in HHT have similar genetic backgrounds to sporadic bAVMs, knowledge gained from bAVMs in HHT may allow us to infer the pathogensis of sporadic bAVMs and to develop new medical therapies from them.

Received February 15, 2016; Accepted March 7, 2016

## Is AVM Congenital or Acquired?

It is classically believed that bAVMs are "congenital" lesions, which means that AVMs exist at birth or exist as a primordial vascular structure due to developmental failure of the embryos in the 40-mm to 80-mm length interval (approximately 10–14 weeks of gestation).[6)] In this context, bAVMs are conceived to be "static" lesions. However, there is little evidence to support this concept. If most bAVMs were "congenital," defined as an existence at birth, phenotypic presentation such as hemorrhage and/or seizure might occur more frequently among younger population. This does not hold true since the average age of the initial diagnosis of bAVMs is about 30–40 years old.[7,8)] The fact that many routinely performed antenatal ultrasound screenings of the fetus fail to detect bAVMs also suggests that developmental AVM formations are rare except for some specific forms of bAVMs such as vein of Galen aneurysmal malformations and dural sinus malformations with arteriovenous (AV) shunts.[9,10)] Increasing evidences support postnatal growth of bAVMs.[11)] De novo formation, growth, regression, recurrence after complete resection, and development

after infarction were infrequently reported.[12–16] These facts indicate a subset of bAVMs is "dynamic" lesions even in adulthood. This means that bAVMs can grow, remodel, and regress in addition to rupture. In fact, as described below, bAVMs do develop in adult-onset mice experimental model under certain conditions.[17,18]

## Sporadic and Familial bAVMs

Most of the bAVMs (more than 95%) are sporadic, but some have apparently genetic backgrounds. It is reported that about 3% of bAVMs are caused by HHT.[19] The HHT and capillary malformation (CM)-AVM are well-known familial bAVMs with known causative gene mutations. Although most familial AVMs are related to HHT, a small number of them are related to CM-AVM, which is caused by mutation of *RASA1* gene.[20] Excluding bAVMs due to these two diseases, familial bAVMs are extremely rare.[21,22] In the latest review of familial bAVMs without HHT, clinical characteristics of familial bAVMs are not significantly different from sporadic bAVMs except for the age at diagnosis. The mean age at diagnosis in 53 patients with familial bAVMs among 25 families was 8 years younger than sporadic bAVMs.[23]

## Single-nucleotide Polymorphisms (SNPs) in bAVMs

The SNPs are variations of deoxyribonucleic acid (DNA) sequence that differ between members of the same species. Evidence of SNPs in sporadic bAVMs has been accumulated (Table 1). Some SNPs in the inflammatory cascades and in the regulation of angiogenesis play a role in the development of hemorrhage of bAVMs nonspecifically. Identification of SNPs related to hemorrhagic risk of bAVMs or bAVM susceptibility enables stratification and prognostication of high-risk patients and selection of the better management.[24,25] Apolipoprotein E (*APOE*) genotype may influence the bleeding risk of bAVMs. APOE ε2 genotype carriers had five-fold increased risk of new hemorrhage than those with the other genotypes.[26] Similarly, SNPs in inflammatory cytokine interleukin-6 (IL-6) (homozygous IL-6 −174G>C) are also associated with hemorrhagic presentation of bAVMs.[27,28] Tumor necrosis factor (TNF)-α is a pro-inflammatory cytokine and TNF-α −238G>A polymorphism is associated with increased risk of hemorrhage in the natural course of bAVMs.[29] activin receptor-like kinase 1 (*ALK1*) intervening sequence (IVS) 3 −35A>G polymorphism is associated with an increased risk (susceptibility) for bAVMs.[30,31] All these genetic associations to hemorrhage and susceptibility of bAVM require replication in larger samples. Recently, Weinsheimer et al. reported genome-wide association study to investigate the association of common SNPs with risk of sporadic bAVM in Caucasians, and found that no SNPs including *ALK1* IVS3 −3A>G were replicated in the large bAVM replication cohort, suggesting that common SNPs do not contribute strongly to bAVM susceptibility.[32]

## Angiogenesis and Inflammation in bAVMs

Molecular and histopathological analysis of bAVM specimen revealed the higher level of angiogenic factors and inflammatory cytokines.[28,33] In fact, angiopoietin-2, matrix metalloproteinase (MMP)-9, vascular endothelial growth factor (VEGF) are highly expressed in sporadic bAVMs, and concerted effects

**Table 1 Bleeding risk or disease susceptibility of single-nucleotide polymorphisms in sporadic brain arteriovenous malformations**

| SNP | Authors | Year | Risk/referent genotype | OR | 95%CI |
|---|---|---|---|---|---|
| Bleeding risk | | | | | |
| IL6 −174G>C | Pawlikowska et al.[27] | 2004 | GG/CC; CG | 2.62 | 1.38–4.98 |
| TNF-α −238G>A | Achrol et al.[29] | 2006 | AG/GG | 4.01 | 1.31–12.29 |
| *APOE* ε2 | Pawlikowska et al.[26] | 2006 | ε2/not ε2 | 4.97 | 1.43–17.3 |
| Disease susceptibility | | | | | |
| *ALK1* IVS3 −35A>G | Pawlikowska et al.[30] | 2005 | AA; AG/GG | 2.47 | 1.38–4.44 |
| | Simon et al.[31] | 2006 | | 1.73 | 1.19–2.51 |

*ALK1*: activin receptor-like kinase 1, *APOE*: apolipoprotein E, CI: confident interval, IL: interleukin, OR: odds ratio, SNP: single-nucleotide polymorphism, TNF: tumor necrosis factor.

of these angiogenic factors may maintain the angiogenic phenotype in bAVMs.[34] Homeobox gene of Hox D3 upregulates the expression of several pro-angiogenic molecules including integrin $\alpha_V ß_3$ and urokinase plasminogen activator and may contribute bAVM formation.[35] Inflammatory cells (neutrophils and macrophages) are also found in bAVMs in the tissue removed during microsurgery.[33] Inflammatory biomarker of IL-6 is increased in bAVMs with hemorrhagic presentation.[36]

## HHT

HHT is an autosomal dominant vascular disorder characterized by vascular dysplasia in multiple organs leading to hemorrhage, stroke, high-output heart failure, and death.[37] It has a prevalence of 1:5,000–8,000.[38,39] For HHT, three gene mutations are known: *endoglin* (*ENG*)[40] for HHT1 (Online Mendelian Inheritance in Man (OMIM) #187300), activin A receptor type II-like kinase 1 (*ACVRL1*) or *ALK1*[41,42] for HHT2 (OMIM #600376) and SMAD family member 4 (*SMAD4*). Gene mutation of *SMAD4* is responsible for a combined syndrome of HHT and juvenile polyposis (OMIM #175050).[43] HHT3 (OMIM #601101) and HHT4 (OMIM #610655) are also described,[44,45] but their genes are not yet identified. Recently, it is reported that mutations in bone morphogenetic protein 9 can cause similar HHT phenotype, thus called HHT5 (OMIM #615506).[46] Clinical variations in HHT are significant with intra- and interfamilial variations in severity of complications, age of onset, and location of the lesions. It is conceivable that sporadic bAVMs may have similar genetic backgrounds to HHT. In this context, HHT is a good clinical and experimental model for the investigation of pathogenesis of bAVMs. Actually, there are many experimental studies using HHT transgenic animals.

### I. Clinical diagnosis of HHT

HHT is caused by gene mutations in transforming growth factor-ß superfamily receptors.[40,41] *ENG* is the causative gene for HHT type 1, and *ALK1* is for HHT type 2. About 85–90% of HHTs are either HHT type 1 or HHT type 2. Small number of HHT is caused by *SMAD4* mutation, which is HHT-related polyposis syndrome. Clinically, HHT is diagnosed by the so-called Curaçao criteria.[47] The following four items of diagnostic criteria show the characteristics of HHT: (1) recurrent, spontaneous nosebleeds; (2) mucocutaneous telangiectasia at tongue, lips, face, fingertips, etc.; (3) visceral AVMs (including AV fistulas) at lungs, brain, liver, and gastrointestinal tract (telangiectasia); and (4) family history of HHT within the first-degree relatives. When patient has more than three items, clinical diagnosis of HHT is definite. Two items are regarded as probable. Only one or no item is regarded as unlikely. Clinico-genetic correlation, in other words, validation of these clinical criteria is very high when adopted to the patients above the age of 16 years.[48]

### II. HHT-related bAVMs: angiographic subtypes

The bAVMs in HHT are morphologically classified into three groups previously: micro-AVMs less than 1 cm in size, regular AVMs usually smaller than 3 cm, and arteriovenous fistulas (AVFs) without nidus.[49] However, recently different classification is proposed: capillary (vascular) malformations, AVMs (with nidus), and AVFs.[50] Capillary malformations have no AV shunts on angiography, but show small stains on angiography and "fluffy" enhancement on gadolinium-enhanced magnetic resonance (MR) images. According to this classification, capillary malformations are the most commonly observed lesions (61%). AVM with nidus less than 1 cm in size (micro-AVM by the previous classification[49]) is classified as AVM if the lesion has a nidus and AV shunts. Hemorrhagic risk of capillary malformations might be very low in contrast to that of AVMs and AVFs. Further accumulation of data on hemorrhagic risk of capillary malformations is necessary to provide appropriate therapeutic indication. In general, bAVMs in HHT have characteristic features of superficial location, small size, and multiple lesions. Especially, multiplicity is a specific feature of HHT-related bAVMs.[19] However, it is impossible to distinguish each HHT-related AVMs from sporadic, non-HHT AVMs on the basis of their angioarchitecture.[49]

### III. Genetic backgrounds of HHT

The *ENG* codes for accessory protein receptors of the TGF-ß receptor complex and *ALK1* encodes for transmembrane kinase which participates the TGF-ß signaling. They are primarily expressed in endothelial cells. *ALK1* regulates endothelial proliferation and migration, and *ENG* promotes *ALK1*'s function in general.[51] Loss-of-function mutations of these genes leading to "haploinsufficiency" are believed to cause HHT. Haploinsufficiency means a reduction of protein to half of the normal levels due to inactivated one copy of gene leading to an abnormal state. However, it is not easy to discriminate polymorphism (benign rare variants) from pathogenic mutations in missense mutations.[52] When pathogenic proteins are expressed, they could also act in dominant-negative fashion, which means

dominant mutation acts in opposition to normal gene function. Since only normal *ENG* is expressed on the cell surface at the level of 50% in HHT type 1, dominant-negative is less likely actually.[53]

### IV. Genotype and phenotype correlations of bAVMs in HHT

Prevalence of HHT type 1- and HHT type 2-related bAVMs is a 1,000- and 100-fold increase, respectively, in comparison to sporadic bAVMs[28] in general population (10/100,000). Gene mutations and their phenotypes in HHT have been investigated to disclose genotype-phenotype correlations. It is known that bAVMs and pulmonary AVFs are more prevalent in HHT type 1 while hepatic AVMs are more prevalent in HHT type 2.[54] There were no clear correlations between genotypes and phenotypes among 109 HHT patients with bAVMs (69% *ENG* mutation, 17% *ALK1* mutation, and 2% *SMAD4* mutation) in terms of age at diagnosis, multiplicity of AVMs, and prevalence of brain hemorrhage, and age at brain hemorrhage among gene groups.[55] Lack of genotype-phenotype correlations in HHT could be attributable to the currently accepted pathogenesis of HHT, that is, "haploinsufficiency," which is not related to the specific modes or sites of gene mutation.

## Animal Models of bAVMs

### I. Classic animal models of bAVMs

Historically, animal AVM models are extradural AV fistulas and are categorized into two types:[56] hemodynamic and angiographic models. In hemodynamic models, AV shunts are created surgically from the contralateral extracranial carotid artery through the circle of Willis to the ipsilateral jugular vein, commonly by anastomosing common carotid artery to ipsilateral jugular vein (creating carotid-jugular fistula) with ligation of the jugular vein distally.[57] In angiographic models, commonly located extracranial "rete mirabile" in artiodactyl (even-toed ungulates) is used as AVM-like structures by surgically created AV shunts.[58] Animal models for interventional neuroradiologic techniques have been used to test various devices and embolic materials. These two types of animal models have no intracranial parenchymal nidus, main difference from bAVMs.[59]

### II. Animal models of HHT-related bAVMs

Transgenic animal models are used for more modern researches on the pathogenesis of bAVMs. Among them, HHT-related transgenic mice are frequently used for this purpose. Two types of animal models are used: developmental (embryological)[42,60] and adult-onset models.[17,18] Knowledge from the genetic pathways in the HHT models can shed light on the pathogenesis of sporadic bAVMs. Expressivity of both *ENG* and *ALK1* mutations is highly variable among HHT family members who share the same mutant alleles, which indicates that other modifying factors might play an important role in disease progression. Such factors are examined by animal models of HHT type 1[60] and HHT type 2[42,61,62] (Table 2).

Homozygous mutation of $ENG^{-/-}$ is lethal at E10–10.5 (embryo at day 10–10.5),[60] which is roughly equivalent to human E24–28. In reality in humans, miscarriage occurred at 6–8 weeks of gestation in consanguineous marriage of two HHT type 1 affected first cousins when *ENG* is essential for cardiovascular development.[63] However, the primitive vasculature of the embryo is normal until E9.0 (equivalent to human E20). This indicates that *ENG* plays an important role in angiogenic process. On the other hand, heterozygous mutation of $ENG^{+/-}$ presents similar symptoms of HHT including nosebleed and telangiectasia in some mice (not all mice) with increasing age, although penetrance is not so high.[64] This implies that HHT type 1 is caused by a loss of function of *ENG*, i.e., haploinsufficiency. If fact, *ENG* level in $ENG^{+/-}$ mouse was about 50% and 3 of 10 mice developed vascular abnormalities including AVM-like structure.[65] Severity and heterogeneity of symptomatology might be associated with the other epigenetic factors such as environment, blood pressure, oxygenation, shear stress, and hormonal levels.[60] Homozygous mutation of $ALK1^{-/-}$ in mice is also lethal at E10.5–11.5, exhibiting severe vascular abnormalities. *ALK1* in endothelial cells played a crucial role in determining vascular endothelial properties during angiogenesis.[51,62] Mice lacking *ALK1* developed large AV shunts at the early stage of vascular development (E9.5).[62]

Heterozygous mice ($ENG^{+/-}$) without stimuli developed less often abnormal microvessel formation than heterozygous mice ($ENG^{+/-}$) stimulated by VEGF.[65,66] $ENG^{+/-}$ mice developed severer cerebrovascular dysplasia than $ALK1^{+/-}$ mice stimulated by VEGF.[67] Inflammatory cells are often found in and around AVMs. Dysmorphic vessels developed in $ENG^{+/-}$ and $ALK1^{+/-}$ mice at the capillary levels, but no AV shunts developed. Although haploinsufficiency of *ENG* or *AlLK1* is popularly accepted to cause HHT, heterozygous mutation of *ENG* or *AlLK1* is not enough to cause bAVM formation.[68] More recently, conditional (tissue and/or time-specific) knockout mice of *ENG* or *ALK1* gene are used as animal models of bAVMs. They have more similarities to human bAVMs in that they have AV shunts and develop spontaneous hemorrhage.[17,18] In the

**Table 2 Mouse models of HHT-related brain AVMs**

| Mutated gene | Authors | Year | Gene deletion hetero/ homozygous | Global/local/ specific cell | Conditional | Developmental/ adult-onset | Stimuli |
|---|---|---|---|---|---|---|---|
| HHT1 | | | | | | | |
| *ENG* | Bourdeau et al.[60] | 1999 | hetero/ homogygous | global | | developmental | |
| *ENG* | Bourdeau et al.[64] | 2001 | heterozygous | global | | developmental | |
| *ENG* | Satomi et al.[65] | 2003 | hetero/ homogygous | global | | developmental | |
| *ENG* | Xu et al.[66] | 2004 | heterozygous | global | | developmental | VEGF |
| *ENG* | Hao et al.[67] | 2010 | heterozygous | global | | developmental | VEGF |
| *ENG* | Choi et al.[68] | 2012 | homozygous | local | conditional | adult-onset | VEGF |
| *ENG* | Choi et al.[18] | 2014 | homozygous | global/smooth muscle cell/ endothelial cell/ macrophage | conditional | adult-onset | VEGF |
| HHT2 | | | | | | | |
| *ALK1* | Oh et al.[61] | 2000 | homozygous | global | | developmental | |
| *ALK1* | Urness et al.[62] | 2000 | homozygous | global | | developmental | |
| *ALK1* | Srinivasan et al.[43] | 2003 | heterozygous | global | | developmental | |
| *ALK1* | Hao et al.[67] | 2010 | heterozygous | global | | developmental | VEGF |
| *ALK1* | Mahmoud et al.[70] | 2010 | homozygous | global | conditional | adult-onset | VEGF |
| *ALK1* | Walker et al.[17] | 2011 | homozygous | local | conditional | adult-onset | VEGF |
| *ALK1* | Choi et al.[68] | 2012 | homozygous | local | conditional | adult-onset | VEGF |
| *ALK1* | Chen et al.[69] | 2014 | homozygous | endothelial cell | conditional | adult-onset | VEGF |

*ALK1*: activin receptor-like kinase 1, *ENG*: endoglin, HHT: hereditary hemorrhagic telangiectasia, VEGF: vascular endothelial growth factor.

experiments using conditional mice with $ENG^{2f/2f}$ global cell types and with $ENG^{2f/2f}$ smooth muscle cell/endothelial cell types, it is concluded that homozygous *ENG* deletion in endothelial cells as well as focal VEGF stimulation might be required for bAVM development.[18] Similarly, deletion of *ALK1* in endothelium alone with focal VEGF stimulation induced bAVM in adult conditional $ALK1^{2f/2f}$ mice.[69] Thus, it seems that homozygous deletion of either *ENG* or *ALK1* in endothelial cells are required for bAVM formation.[18,56,69,70]

## Factors Contributing to Pathogenesis of bAVMs

It is known that higher levels of angiogenic factors and inflammatory cytokines are observed in bAVMs than in the normal brain tissues.[33,36] Also, inflammatory cells are infiltrated to bAVMs.[33] Minor trauma, ischemia, venous hypertension, exogeneous growth factor delivery, high endogenous angiogenic factors, inflammation, and infection are known angiogenic factors contributing to manifest bAVMs.[33,36,66,67]

In HHT, development of AVMs may require a copy of inherited mutated gene in particular cells, first. And then, a second hit by the focal somatic mutation in another copy of gene may result in AVM formation in that lesion,[71] as occurred in cerebral cavernous malformation and venous malformation ("second-hit" model).[72–75] Alternatively, the second hit could be "environmental" in the form of a localized physiological or pathological perturbation.[70,75] Shedding of *ENG* from endothelial cells during inflammation,[70] reduced endothelial *ENG* signaling due to increased soluble *ENG* level,[76] and altered blood flow which precipitates a flow-dependent adaptive response involving retention of normally transient AV connections[77] are the examples.

From insights into these current bAVM models, it is suggested that both angiogenic stimulation (environmental factors) and regional conditional homozygous gene deletion (genetic predisposition) may promote the ideal bAVM development in the adult mouse brain.[17,78]

## Conclusion

Although pathogenesis of bAVMs is not clearly understood, many researches are underway, especially using HHT animal models. Knowledge from such research works may help deeper understanding of the pathogenesis and provide novel therapeutic approaches to bAVMs in the near future.

## Conflicts of Interest Disclosure

The author has no conflicts of interest with regard to this manuscript and has registered online Self-reported COI Disclosure Statement Forms through the website for The Japan Neurosurgical Society members.

## References

1) van Beijnum J, van der Worp HB, Buis DR, Al-Shahi Salman R, Kappelle LJ, Rinkel GJ, van der Sprenkel JW, Vandertop WP, Algra A, Klijn CJ: Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. *JAMA* 306: 2011–2019, 2011
2) Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, Al-Shahi Salman R, Vicaut E, Young WL, Houdart E, Cordonnier C, Stefani MA, Hartmann A, von Kummer R, Biondi A, Berkefeld J, Klijn CJ, Harkness K, Libman R, Barreau X, Moskowitz AJ; international ARUBA investigators: Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet* 383: 614–621, 2014
3) Rendu H: Epistaxis répétées chez un sujet porteur de petits angiomes cutanes et muqueux. *Gaz Soc Hosp* (*Paris*) 69: 1322–1323, 1896
4) Osler W: On a family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes. *Bull Johns Hopkins Hos* 12: 333–337, 1901
5) Weber FP: Multiple hereditary developmental angiomata of the skin and mucous membranes associated with recurring haemorrhages. *Lancet* 2: 160–162, 1907
6) Mullan S, Mojtahedi S, Johnson DL, Macdonald RL: Embryological basis of some aspects of cerebral vascular fistulas and malformations. *J Neurosurg* 85: 1–8, 1996
7) Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP; Scottish Intracranial Vascular Malformation Study Collaborators: Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke* 34: 1163–1169, 2003
8) Stapf C, Mast H, Sciacca RR, Berenstein A, Nelson PK, Gobin YP, Pile-Spellman J, Mohr JP; New York Islands AVM Study Collaborators: The New York Islands AVM Study: design, study progress, and initial results. *Stroke* 34: e29–e33, 2003
9) Komiyama M, Nakajima H, Nishikawa M, Kitano S, Sakamoto H: Interventional neuroangiography in neonates. *Interv Neuroradiol* 5(Suppl 1): 127–132, 1999
10) Komiyama M, Ishiguro T, Kitano S, Sakamoto H, Nakamura H: Serial antenatal sonographic observation of cerebral dural sinus malformation. *AJNR Am J Neuroradiol* 25: 1446–1448, 2004
11) Komiyama M: Revised perspective of cerebral arteriovenous malformations. *Jpn J Neurosurg* (*Tokyo*) 20: 4–11, 2011 (Japanese)
12) Schmit BP, Burrows PE, Kuban K, Goumnerova L, Scott RM: Acquired cerebral arteriovenous malformation in a child with moyamoya disease. Case report. *J Neurosurg* 84: 677–680, 1996
13) Friedman JA, Pollock BE, Nichols DA: Development of a cerebral arteriovenous malformation documented in an adult by serial angiography. Case report. *J Neurosurg* 93: 1058–1061, 2000
14) Miyasaka Y, Nakahara K, Takagi H, Hagiwara H: Development of multiple cerebral arteriovenous malformations documented in an adult by serial angiography. Case report. *J Neurosurg* 98: 190–193, 2003
15) Du R, Hashimoto T, Tihan T, Young WL, Perry V, Lawton MT: Growth and regression of arteriovenous malformations in a patient with hereditary hemorrhagic telangiectasia. Case report. *J Neurosurg* 106: 470–477, 2007
16) Shimoda Y, Osanai T, Nakayama N, Ushikoshi S, Hokari M, Shichinohe H, Abumiya T, Kazumata K, Houkin K: De novo arteriovenous malformation in a patient with hereditary hemorrhagic telangiectasia. *J Neurosurg Pediatr* 17: 330–335, 2016
17) Walker EJ, Su H, Shen F, Choi EJ, Oh SP, Chen G, Lawton MT, Kim H, Chen Y, Chen W, Young WL: Arteriovenous malformation in the adult mouse brain resembling the human disease. *Ann Neurol* 69: 954–962, 2011
18) Choi EJ, Chen W, Jun K, Arthur HM, Young WL, Su H: Novel brain arteriovenous malformation mouse models for type 1 hereditary hemorrhagic telangiectasia. *PLoS ONE* 9: e88511, 2014
19) Bharatha A, Faughnan ME, Kim H, Pourmohamad T, Krings T, Bayrak-Toydemir P, Pawlikowska L, McCulloch CE, Lawton MT, Dowd CF, Young WL, Terbrugge KG: Brain arteriovenous malformation multiplicity predicts the diagnosis of hereditary hemorrhagic telangiectasia: quantitative assessment. *Stroke* 43: 72–78, 2012

20) Revencu N, Boon LM, Mulliken JB, Enjolras O, Cordisco MR, Burrows PE, Clapuyt P, Hammer F, Dubois J, Baselga E, Brancati F, Carder R, Quintal JM, Dallapiccola B, Fischer G, Frieden IJ, Garzon M, Harper J, Johnson-Patel J, Labrèze C, Martorell L, Paltiel HJ, Pohl A, Prendiville J, Quere I, Siegel DH, Valente EM, Van Hagen A, Van Hest L, Vaux KK, Vicente A, Weibel L, Chitayat D, Vikkula M: Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Hum Mutat* 29: 959–965, 2008
21) Yokoyama K, Asano Y, Murakawa T, Takada M, Ando T, Sakai N, Yamada H, Iwata H: Familial occurrence of arteriovenous malformation of the brain. *J Neruosurg* 74: 585–589, 1991
22) Inoue S, Liu W, Inoue K, Mineharu Y, Takenaka K, Yamakawa H, Abe M, Jafar JJ, Herzig R, Koizumi A: Combination of linkage and association studies for brain arteriovenous malformation. *Stroke* 38: 1368–1370, 2007
23) van Beijnum J, van der Worp HB, Schippers HM, van Nieuwenhuizen O, Kappelle LJ, Rinkel GJ, Berkelbach van der Sprenkel JW, Klijn CJ: Familial occurrence of brain arteriovenous malformations: a systematic review. *J Neurol Neurosurg Psychiatr* 78: 1213–1217, 2007
24) Young WL, Yang GY: Are there genetic influences on sporadic brain arteriovenous malformations? *Stroke* 35: 2740–2745, 2004
25) Sturiale CL, Puca A, Sebastiani P, Gatto I, Albanese A, Di Rocco C, Maira G, Pola R: Single nucleotide polymorphisms associated with sporadic brain arteriovenous malformations: where do we stand? *Brain* 136: 665–681, 2013
26) Pawlikowska L, Poon KY, Achrol AS, McCulloch CE, Ha C, Lum K, Zaroff JG, Ko NU, Johnston SC, Sidney S, Marchuk DA, Lawton MT, Kwok PY, Young WL: Apolipoprotein E epsilon 2 is associated with new hemorrhage risk in brain arteriovenous malformations. *Neurosurgery* 58: 838–843; discussion 838–843, 2006
27) Pawlikowska L, Tran MN, Achrol AS, McCulloch CE, Ha C, Lind DL, Hashimoto T, Zaroff J, Lawton MT, Marchuk DA, Kwok PY, Young WL; UCSF BAVM Study Project: Polymorphisms in genes involved in inflammatory and angiogenic pathways and the risk of hemorrhagic presentation of brain arteriovenous malformations. *Stroke* 35: 2294–2300, 2004
28) Kim H, Marchuk DA, Pawlikowska L, Chen Y, Su H, Yang GY, Young WL: Genetic considerations relevant to intracranial hemorrhage and brain arteriovenous malformations. *Acta Neurochir Suppl* 105: 199–206, 2008
29) Achrol AS, Pawlikowska L, McCulloch CE, Poon KY, Ha C, Zaroff JG, Johnston SC, Lee C, Lawton MT, Sidney S, Marchuk DA, Kwok PY, Young WL; UCSF BAVM Study Project: Tumor necrosis factor-alpha-238G>A promoter polymorphism is associated with increased risk of new hemorrhage in the natural course of patients with brain arteriovenous malformations. *Stroke* 37: 231–234, 2006
30) Pawlikowska L, Tran MN, Achrol AS, Ha C, Burchard E, Choudhry S, Zaroff J, Lawton MT, Castro R, McCulloch CE, Marchuk D, Kwok PY, Young WL; UCSF BAVM Study Project: Polymorphisms in transforming growth factor-beta-related genes ALK1 and ENG are associated with sporadic brain arteriovenous malformations. *Stroke* 36: 2278–2280, 2005
31) Simon M, Franke D, Ludwig M, Aliashkevich AF, Köster G, Oldenburg J, Boström A, Ziegler A, Schramm J: Association of a polymorphism of the ACVRL1 gene with sporadic arteriovenous malformations of the central nervous system. *J Neurosurg* 104: 945–949, 2006
32) Weinsheimer S, Bendjilali N, Nelson J, Guo DE, Zaroff JG, Sidney S, McCulloch CE, Al-Shahi Salman R, Berg JN, Koeleman BP, Simon M, Bostroem A, Fontanella M, Sturiale CL, Pola R, Puca A, Lawton MT, Young WL, Pawlikowska L, Klijn CJ, Kim H; GEN-AVM Consortium: Genome-wide association study of sporadic brain arteriovenous malformations. *J Neurol Neurosurg Psychiatry* pii: jnnp-2015-312272, 2016 [Epub ahead of print]
33) Chen Y, Zhu W, Bollen AW, Lawton MT, Barbaro NM, Dowd CF, Hashimoto T, Yang GY, Young WL: Evidence of inflammatory cell involvement in brain arteriovenous malformations. *Neurosurgery* 62: 1340–1349; *discussion* 1349–1350, 2008
34) Hashimoto T, Wu Y, Lawton MT, Yang GY, Barbaro NM, Young WL: Coexpression of angiogenic factors in brain arteriovenous malformations. *Neurosurgery* 56: 1058–1065; discussion 1058–1065, 2005
35) Chen Y, Xu B, Arderiu G, Hashimoto T, Young WL, Boudreau N, Yang GY: Retroviral delivery of homeobox D3 gene induces cerebral angiogenesis in mice. *J Cereb Blood Flow Metab* 24: 1280–1287, 2004
36) Chen Y, Pawlikowska L, Yao JS, Shen F, Zhai W, Achrol AS, Lawton MT, Kwok PY, Yang GY, Young WL: Interleukin-6 involvement in brain arteriovenous malformations. *Ann Neurol* 59: 72–80, 2006
37) Shovlin CL: Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment. *Blood Rev* 24: 203–219, 2010
38) Kjeldsen AD, Vase P, Green A: Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. *J Intern Med* 245: 31–39, 1999
39) Dakeishi M, Shioya T, Wada Y, Shindo T, Otaka K, Manabe M, Nozaki J, Inoue S, Koizumi A: Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum Mutat* 19: 140–148, 2002
40) McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J: Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet* 8: 345–351, 1994
41) Johnson DW, Berg JN, Gallione CJ, McAllister KA, Warner JP, Helmbold EA, Markel DS, Jackson CE,

Porteous ME, Marchuk DA: A second locus for hereditary hemorrhagic telangiectasia maps to chromosome 12. *Genome Res* 5: 21–28, 1995
42) Srinivasan S, Hanes MA, Dickens T, Porteous ME, Oh SP, Hale LP, Marchuk DA: A mouse model for hereditary hemorrhagic telangiectasia (HHT) type 2. *Hum Mol Genet* 12: 473–482, 2003
43) Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA: A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* 363: 852–859, 2004
44) Cole SG, Begbie ME, Wallace GM, Shovlin CL: A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. *J Med Genet* 42: 577–582, 2005
45) Bayrak-Toydemir P, McDonald J, Akarsu N, Toydemir RM, Calderon F, Tuncali T, Tang W, Miller F, Mao R: A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. *Am J Med Genet A* 140: 2155–2162, 2006
46) Wooderchak-Donahue WL, McDonald J, O'Fallon B, Upton PD, Li W, Roman BL, Young S, Plant P, Fülöp GT, Langa C, Morrell NW, Botella LM, Bernabeu C, Stevenson DA, Runo JR, Bayrak-Toydemir P: BMP9 mutations cause a vascular-anomaly syndrome with phenotypic overlap with hereditary hemorrhagic telangiectasia. *Am J Hum Gen* 93: 530–537, 2013
47) Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H: Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 91: 66–67, 2000
48) van Gent MW, Velthuis S, Post MC, Snijder RJ, Westermann CJ, Letteboer TG, Mager JJ: Hereditary hemorrhagic telangiectasia: how accurate are the clinical criteria? *Am J Med Genet A* 161A: 461–466, 2013
49) Matsubara S, Mandzia JL, ter Brugge K, Willinsky RA, Faughnan ME, Manzia JL: Angiographic and clinical characteristics of patients with cerebral arteriovenous malformations associated with hereditary hemorrhagic telangiectasia. *AJNR Am J Neuroradiol* 21: 1016–1020, 2000
50) Krings T, Kim H, Power S, Nelson J, Faughnan ME, Young WL, terBrugge KG; Brain Vascular Malformation Consortium HHT Investigator Group: Neurovascular manifestations in hereditary hemorrhagic telangiectasia: imaging features and genotype-phenotype correlations. *AJNR Am J Neuroradiol* 36: 863–870, 2015
51) Lebrin F, Deckers M, Bertolino P, Ten Dijke P: TGF-beta receptor function in the endothelium. *Cardiovasc Res* 65: 599–608, 2005
52) Mallet C, Lamribet K, Giraud S, Dupuis-Girod S, Feige JJ, Bailly S, Tillet E: Functional analysis of endoglin mutations from hereditary hemorrhagic telangiectasia type 1 patients reveals different mechanisms for endoglin loss of function. *Hum Mol Genet* 24: 1142–1154, 2015
53) Pece N, Vera S, Cymerman U, White RI Jr, Wrana JL, Letarte M: Mutant endoglin in hereditary hemorrhagic telangiectasia type 1 is transiently expressed intracellularly and is not a dominant negative. *J Clin Invest* 100: 2568–2579, 1997
54) Komiyama M, Ishiguro T, Yamada O, Morisaki H, Morisaki T: Hereditary hemorrhagic telangiectasia in Japanese patients. *J Hum Genet* 59: 37–41, 2014
55) Nishida T, Faughnan ME, Krings T, Chakinala M, Gossage JR, Young WL, Kim H, Pourmohamad T, Henderson KJ, Schrum SD, James M, Quinnine N, Bharatha A, Terbrugge KG, White RI Jr: Brain arteriovenous malformations associated with hereditary hemorrhagic telangiectasia: gene-phenotype correlations. *Am J Med Genet A* 158A: 2829–2834, 2012
56) Chen W, Choi EJ, McDougall CM, Su H: Brain arteriovenous malformation modeling, pathogenesis, and novel therapeutic targets. *Transl Stroke Res* 5: 316–329, 2014
57) Terada T, Higashida RT, Halbach VV, Dowd CF, Tsuura M, Komai N, Wilson CB, Hieshima GB: Development of acquired arteriovenous fistulas in rats due to venous hypertension. *J Neurosurg* 80: 884–889, 1994
58) Chaloupka JC, Viñuela F, Robert J, Duckwiler GR: An in vivo arteriovenous malformation model in swine: preliminary feasibility and natural history study. *AJNR Am J Neuroradiol* 15: 945–950, 1994
59) TerBrugge KG, Lasjaunias P, Hallacq P: Experimental models in interventional neuroradiology. *AJNR Am J Neuroradiol* 12: 1029–1033, 1991
60) Bourdeau A, Dumont DJ, Letarte M: A murine model of hereditary hemorrhagic telangiectasia. *J Clin Invest* 104: 1343–1351, 1999
61) Oh SP, Seki T, Goss KA, Imamura T, Yi Y, Donahoe PK, Li L, Miyazono K, ten Dijke P, Kim S, Li E: Activin receptor-like kinase 1 modulates transforming growth factor-beta 1 signaling in the regulation of angiogenesis. *Proc Natl Acad Sci USA* 97: 2626–2631, 2000
62) Urness LD, Sorensen LK, Li DY: Arteriovenous malformations in mice lacking activin receptor-like kinase-1. *Nat Genet* 26: 328–331, 2000
63) Karabegovic A, Shinawi M, Cymerman U, Letarte M: No live individual homozygous for a novel endoglin mutation was found in a consanguineous Arab family with hereditary haemorrhagic telangiectasia. *J Med Genet* 41: e119, 2004
64) Bourdeau A, Faughnan ME, McDonald ML, Paterson AD, Wanless IR, Letarte M: Potential role of modifier genes influencing transforming growth factor-beta1 levels in the development of vascular defects in endoglin heterozygous mice with hereditary hemorrhagic telangiectasia. *Am J Pathol* 158: 2011–2020, 2001
65) Satomi J, Mount RJ, Toporsian M, Paterson AD, Wallace MC, Harrison RV, Letarte M: Cerebral vascular abnormalities in a murine model of hereditary hemorrhagic telangiectasia. *Stroke* 34: 783–789, 2003
66) Xu B, Wu YQ, Huey M, Arthur HM, Marchuk DA, Hashimoto T, Young WL, Yang GY: Vascular endothelial growth factor induces abnormal microvasculature

in the endoglin heterozygous mouse brain. *J Cereb Blood Flow Metab* 24: 237–244, 2004
67) Hao Qi, Zhu Y, Su H, Shen F, Yang GY, Kim H, Young WL: VEGF induces more severe cerebrovascular dysplasia in endoglin than in Alk1 mice. *Trans Stroke Res* 1: 197–201, 2010
68) Choi EJ, Walker EJ, Shen F, Oh SP, Arthur HM, Young WL, Su H: Minimal homozygous endothelial deletion of Eng with VEGF stimulation is sufficient to cause cerebrovascular dysplasia in the adult mouse. *Cerebrovasc Dis* 33: 540–547, 2012
69) Chen W, Sun Z, Han Z, Jun K, Camus M, Wankhede M, Mao L, Arnold T, Young WL, Su H: De novo cerebrovascular malformation in the adult mouse after endothelial Alk1 deletion and angiogenic stimulation. *Stroke* 45: 900–902, 2014
70) Mahmoud M, Allinson KR, Zhai Z, Oakenfull R, Ghandi P, Adams RH, Fruttiger M, Arthur HM: Pathogenesis of arteriovenous malformations in the absence of endoglin. *Circ Res* 106: 1425–1433, 2010
71) Garrido-Martin EM, Nguyen HL, Cunningham TA, Choe SW, Jiang Z, Arthur HM, Lee YJ, Oh SP: Common and distinctive pathogenetic features of arteriovenous malformations in hereditary hemorrhagic telangiectasia 1 and hereditary hemorrhagic telangiectasia 2 animal models—brief report. *Arterioscler Thromb Vasc Biol* 34: 2232–2236, 2014
72) Gault J, Shenkar R, Recksiek P, Awad IA: Biallelic somatic and germ line CCM1 truncating mutations in a cerebral cavernous malformation lesion. *Stroke* 36: 872–874, 2005
73) Brouillard P, Vikkula M: Genetic causes of vascular malformations. *Hum Mol Genet* 16(Spec No 2):R140–R149, 2007
74) Akers AL, Johnson E, Steinberg GK, Zabramski JM, Marchuk DA: Biallelic somatic and germline mutations in cerebral cavernous malformations (CCMs): evidence for a two-hit mechanism of CCM pathogenesis. *Hum Mol Genet* 18: 919–930, 2009
75) Leblanc GG, Golanov E, Awad IA, Young WL; Biology of Vascular Malformations of the Brain NINDS Workshop Collaborators: Biology of vascular malformations of the brain. *Stroke* 40: e694–e702, 2009
76) Chen Y, Hao Q, Kim H, Su H, Letarte M, Karumanchi SA, Lawton MT, Barbaro NM, Yang GY, Young WL: Soluble endoglin modulates aberrant cerebral vascular remodeling. *Ann Neurol* 66: 19–27, 2009
77) Corti P, Young S, Chen CY, Patrick MJ, Rochon ER, Pekkan K, Roman BL: Interaction between alk1 and blood flow in the development of arteriovenous malformations. *Development* 138: 1573–1582, 2011
78) Kim H, Su H, Weinsheimer S, Pawlikowska L, Young WL: Brain arteriovenous malformation pathogenesis: a response-to-injury paradigm. *Acta Neurochir Suppl* 111: 83–92, 2011

---

*Address reprint requests to*: Masaki Komiyama, MD, Department of Neuro-Intervention, Osaka City General Hospital, 2-13-22 Miyakojima-Hondori, Miyakojima, Osaka, Osaka 534-0021, Japan.
*e-mail: komiyama@japan-mail.com*