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An updated review on the genetics of arteriovenous malformations

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Abstract

Arteriovenous malformations (AVM) are congenital malformations of the cerebral vasculature resulting in pathological shunting of blood through dilated arteries and veins. The most common clinical manifestations of AVM are intracerebral hemorrhage, due to rupture of these lesions as they continue to expand, which can have devastating neurological consequences and residual deficits. The genetic underpinnings of AVM have been explored for their role in the angiogenesis of these lesions in both its sporadic and inherited forms. In recent times, our understanding of the genetic variation involved in the pathogenesis AVM has advanced in both the preclinical and clinical realms. The current review highlights in detail these advancements, namely, the genetic underpinnings of diagnostic testing and profiling of AVM, and the preclinical epigenetic and genetic data on AVM pathogenesis and growth. In addition, we review the current candidate genes implicated in AVM pathogenesis in the literature. Finally, we provide a discussion on the genetic conditions associated with AVM and the advancements in treatment paradigms influenced by the genetic profiles of these lesions.

Keywords

Arteriovenous malformations; Intracerebral hemorrhage; Genetics; Capillary malformations

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1. Introduction

Arteriovenous malformations of the brain (bAVM) have long presented a unique challenge to clinicians. An arteriovenous malformation (AVM) is typically defined as an unusual or abnormal shunt bypassing the capillary bed and connecting an artery and a vein[1]. Depending on their location and development, rupture of these congenital vasculature connections can result in many complications, including abscess, hypoxia, and even intracranial hemorrhage (ICH) (Figure 1). Most treatment is aimed at surgically correcting the bAVM, often through various means involving embolization, resection, or, more recently, controlled doses of radiation[2,3]. Although these interventions prove effective, with the most notable being recanalization, complications can persist, more frequently in cerebral AVM[4,5]. Surgical intervention may also simply be less beneficial in a patient with multiple bAVM or a smaller, less focal malformation. For these and other individuals, medical management is key, yet there remains a dearth of medical therapies available for bAVM[6]. This is due to ambiguity surrounding its pathophysiology[7]. While much has been suggested in terms of the etiology of the anomaly, no causative factor has been identified.

What is clear from the available evidence is that genetics play a key role in AVM development, and with advances in technology and DNA sequencing techniques, the genetic underpinnings of bAVM are now more than ever much more easily studied[6,8]. Mutations in genes related to inflammation or angiogenesis, for example, have been identified for associations with bAVM and ICH. These candidate genes are diverse, affecting pathways like interleukin (IL)-6 signaling and endothelial remodeling. Overexpression of vascular endothelial growth factor (VEGF), for instance, has been linked to increased hemorrhaging in bAVM[9]. In addition to this, another focus of study has been examining already characterized genetic syndromes that present with bAVM, like hereditary hemorrhagic telangiectasia (HHT), which often comprises most familial cases of the condition[10]. The hope is that by understanding these Mendelian diseases, we will gain insight into the pathogenesis of bAVM.

Clearly, we have advanced and will continue to advance in our understanding of the genetics of bAVM. However, while there is much in the literature in the way of specific gene associations and syndromes, there is a lack of comprehensive reviews overviewing the genetic underpinnings of the condition. Such an overview would allow for a better understanding of bAVM and its genetic associations. Thus, in the following paper, we aim to remedy that gap, highlighting the etiology of bAVM, with a special focus on preclinical and clinical studies examining its genetic basis. We also generally review candidate genes thought to be involved in bAVM pathology and consider relevant syndromes and diseases. We end our discussion with a thorough analysis of emerging treatment options for bAVM, based on its genetic profile.

2. Etiology and pathogenesis of AVM

2.1. Etiology and epidemiology

bAVM is twisted networks of blood vessels derived from abnormal capillary network development which leads to direct connections between cerebral arteries and veins[11]. They

can be characterized by one or more arterial pedicles feeding into a vascular nidus creating early drainage into a venous outflow channel (Figure 1)[12]. bAVM is rare anomalies but generally are not present at birth and take time to develop[13]. Although bAVM is originally thought to be congenital, continued research and increasing evidence may indicate that bAVM is acquired and likely involves environmental and genetic influences. Some studies have shown that neurogenic locus notch homolog 4 single nucleotide polymorphisms (SNPs) could potentially be a genetic risk factor involved in the development, presentation, and pathogenesis of bAVM[14]. Risk factors for developing bAVM are largely unknown but inflammation has been linked to the progression of bAVM[15].

bAVM is estimated to be in approximately 0.05% of the population and is detected in about one in every 100,000 people[16]. bAVM can be asymptomatic but commonly present with ICH or seizure[11,12,17]. bAVM is the leading cause of ICH in children and young adults[18]. Over half of those detected will first present with hemorrhage[13,16]. Of those that do have symptoms presentation usually appears between the second and third decade of life. These findings are particularly of value because previous hemorrhage is the most important indicator for subsequent hemorrhage[19]. Hemorrhage and recurrence of hemorrhage make bAVM a serious condition for younger adults especially. bAVM can be associated with concurrent aneurysms, further increasing the risk of hemorrhage[20,21]. Specific aneurysms linked to an increased risk of hemorrhage are feeding artery and intranidal aneurysms[21]. In a univariate analysis, it was indicated that feeding arterial aneurysms are independent determinants for an increased risk of hemorrhage (hazard ratio [HR] = 1.78, 95% confidence interval [CI] = 0.91–3.46)[22]. Other symptoms of bAVM may include focal neurologic deficits and headaches[11,12]. Large midline AVM that drain into the vein of Galen can form but are not considered true AVM and are classified as vein of Galen malformations[17]. These malformations exclusively occur in children, and typically present with hydrocephalus, congestive heart failure, and prominent forehead veins[17].

The causes of bAVM are mostly unknown, but recent studies have shown that abnormal expression of angiogenic and inflammatory proteins associated with somatic gene mutations are linked to increased AVM susceptibility and hemorrhage[13]. Mullan noticed that venous malformations and bAVM shared some similarities, and hypothesized that venous malformations and bAVM could be developmentally linked and that bAVM were fistulized venous malformations that developed during embryogenesis[23]. Mullan based the theory on the treatment of venous malformations and bAVM because venous side occlusion is more curative than the arterial side in both conditions[23]. Approximately 95% of bAVM are sporadic while the rest can be linked to hereditary conditions, with HHT being the most common condition[16].

2.2. Diagnosis and treatment

Magnetic resonance imaging (MRI) and computed tomography (CT) are important tools for the characterization of bAVM. During 3D multidetector CT, bAVM can show a spot sign which is seen when contrast leaks out the blood vessel wall[13]. In contrast-enhanced, CT a key distinguishing feature is the “serpentine enhancement pattern[13].” MRI with MR angiography and CT angiography is best for identifying the size, location, history, and risk

of hemorrhage, the mass effect of the lesion, and prognosis[24]. Treating bAVM tends to be clinically challenging and requires a variety of resources[18]. Microsurgical resection, stereotactic radiosurgery, and endovascular embolization are options for treating bAVM and may be used individually or in combination[18]. The complex nature of bAVM typically requires multiple imaging and treatment modalities for adequate clinical care[13,18,24]. The goal of treating AVM is usually to prevent hemorrhage and manage symptoms[25]. Findings from a meta-analysis indicated that all three treatment options were associated with significant risks and low efficacy. In addition, multi-modal approaches may be the safest option, but they are still associated with the combined risks of each approach[25].

Some may classify bAVM into three categories: Parenchymal AVM, pure dural AVM, and mixed parenchymal and dural AVM. In addition, parenchymal AVM includes four subcategories: Pial, subcortical, paraventricular, and combined[17]. In this paper, we focus on parenchymal AVM. The Spetzler-Martin Grading System was designed by Spetzler and Martin to associate major AVM characteristics with risks for surgical intervention[13]. The Spetzler-Martin Grading System has three components: Size, eloquence of the adjacent brain, and pattern of venous drainage[17]. The scale ranges from 1 to 5, and the grade of the AVM is determined by adding the score of each component. You can receive up to 3 points for the size of the AVM and up to 1 point for the other components[17]. Lower grades predict better success with surgical intervention. Spetzler did not recommend surgical intervention for Grade 4 or 5 lesions[17]. Unofficially, there is also a Grade 6 that describes an inoperable AVM[3,5]. The Spetzler-Martin Grading System, initially published in 1986, is commonly used today, and at present, there are many variations and modifications which try to compensate for the variability of Grade 3 AVM[17,25]. There have been many proposed classification systems to assess the risk of endovascular and stereotactic radiosurgical approaches to treat bAVM. Pollock *et al.* compared five AVM grading scales useful for predicting stereotactic radiosurgical outcomes[26]. Those grading scales were the Spetzler-Martin grading scale, radiosurgery-based AVM score (RBAS), Heidelberg score, virginia radiosurgery AVM scale (VRAS), and proton radiosurgery AVM scale (PRAS)[26]. They found that continuous scores such as RBAS and PRAS were more accurate than the Spetzler-Martin Grading System[26]. Although there have been several proposed scales to use for endovascular surgery, none have become widely popular[25]. Jin *et al.* found that the Puerto Rico score did a better job of predicting complications in endovascular surgery than the Spetzler-Martin Grading system[27].

Altogether, understanding the etiology, pathogenesis, diagnosis, and treatment of AVM requires a multifunctional perspective. A more detailed look at the cellular and molecular physiology of AVM pathogenesis has more recently allowed for the identification of key signaling mediators in AVM angiogenesis, which we will discuss further.

3. Molecular characterization of AVM pathogenesis

3.1. Pathogenesis

The pathogenesis of bAVM is not fully understood. Some well-known associated factors such as angiogenic factors and inflammatory cytokines likely influence the development of bAVM[28]. Chen *et al.* demonstrated that inflammatory cells were present

in bAVM, indicating that inflammation may be involved in disease progression or pathogenesis[29]. Molecular and histopathological characterization of bAVM tissue showed increased expression of angiogenic factors, such as VEGF, angiopoietin-2, and matrix metalloproteinase (MMP)-9 as well as elevated expression of inflammatory factors, such as IL-6 and Myeloperoxidase (MPO)[30]. Kim *et al.* speculated that bAVM develops from regions destined to become the AVM nidus and some inciting event would cause an increase in angiogenic factors or inflammatory cytokines. Instead of stabilizing like normal vessels, this predestined area undergoes a dysplastic response and over time will eventually develop into bAVM nidus[30].

Previous studies focused on somatic mutations and genetic abnormalities have revealed promising findings allowing for a better understanding of the development of bAVM. Mukhtarova *et al.* identified a pathogenic sirtuin 1 (*SIRT1*) variant that could be linked to a molecular mechanism in bAVM development[31]. According to Mukhtarova *et al.*, *SIRT1* is expressed in the blood vessels during development and is important for angiogenesis[31]. They found that when *SIRT1* was impaired in mice and zebrafish, it led to abnormal blood vessel formation[31]. In another study, Yan *et al.* found that the mammalian target of rapamycin - fatty acid-binding protein 4 (mTOR-FABP4) signal was activated in bAVM[32]. They noted that the mTOR-FABP4 pathway plays a role in several endothelial cell processes such as proliferation, apoptosis, migration, and vascular tube formation. Finding mTOR-FABP4 pathway activation in bAVM indicates that mTOR pathway inhibitors could potentially be implicated in future treatment[32]. Other gene mutations found in bAVM include the Kirsten rat sarcoma virus (*KRAS*) and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations. Bameri *et al.* found in a systematic literature review that in 1726 patients with bAVM, 55% had *KRAS* mutations and 7.5% had *BRAF* mutations[33]. Both the *KRAS* and *BRAF* mutations are associated with cancers and tumor growth, but in bAVM, they may be linked to endothelial proliferation, angiogenic signaling, or vascular remodeling process[33].

3.2. Genetics of molecular mechanism of pathogenesis

More recently, next generation sequencing (NGS) technologies have allowed for multiple studies to examine the genetic basis of AVM pathogenesis. While our understanding at this level is still limited, we will discuss the current literature on the molecular mechanisms of AVM angiogenesis. The two greatest areas of attention for research have focused on (i) the family linkage analysis in patients with AVM and (ii) the analysis of the defective genes using post-operative specimens[34].

Scimone *et al.* conducted a study using whole exome sequencing on a young boy with sporadic bAVM to identify a set of novel gene-disrupting variants implicated in vascular differentiation[35]. They proposed a set of 20 gene-disrupting variants, which are potentially involved in AVM pathogenesis, of which 1 is non-sense mutation, 2 are splice-affecting variants, and 17 are missense mutations. The list of candidate loci they proposed for future study in AVM pathogenesis included: NBPF member 10 (*NBPF10*), Ephrin A4 (*EFNA4*), NAD(P)HX epimerase (*NAXE*), tetratricopeptide repeat domain 21B (*TTC21B*), bone morphogenetic protein 3 (*BMP3*), insulin like growth factor binding protein 7 (*IGFBP7*), slit

guidance ligand 2 (*SLIT2*), CD109 molecule (*CD109*), tenascin XB (*TNXB*), chondroitin sulfate proteoglycan 4 (*CSPG4*), amine oxidase copper containing 3 (*AOC3*), NEDD4 like E3 ubiquitin protein ligase (*NEDD4L*), serine/threonine kinase 4 (*STK4*), and fibronectin leucine rich transmembrane protein 3 (*FLRT3*). The major classification categories of these variants were defined by their involvement in transforming growth factor beta 1-suppressor of mothers against decapentaplegic (TGF-β/SMAD) transduction pathway, and the regulation of angiogenetic process and arterial and venous differentiation. While most of their discovered variants have yet to be associated with clinical significance in the literature, they proposed that the *de novo* c.569G > A (p.Trp190Ter) nonsense mutation affecting the *STK4* gene could be involved in the AVM phenotype development. This variant was uniquely found in their AVM patient and not in the familial cohort who were also tested. In addition, in the literature, *STK4* has been implicated in blood vessel branching and morphogenesis[35,36]. Thus, continued NGS studies have helped identify unique genetic markers associated with AVM which can later be correlated with their role in pathogenesis.

bAVM has also been reported to overexpress genes which play a regulatory role in essential processes of angiogenesis and lymphogenesis. In a study examining human AVM tissue, Shoemaker *et al.* identified these set of AVM unique genes, including COUP transcription factor 2 (*COUP-TFII*), SRY-box transcription factor 18 (*SOX18*), prospero homeobox 1 (*PROX1*), nuclear factor of activated T cells 1 (*NFATC1*), forkhead box C2 *(FOXC2),* T-box transcription factor 1 (*TBX1*), lymphatic vessel endothelial hyaluronan receptor *1* (*LYVE1*), *Podoplanin*, and *VEGFC*. In addition, these expressed genes were correlated with clinical edema and acute hemorrhage[37]. This assembly of complex genes implies that the signaling pathway of AVM formation and proliferation is also complex, and future studies are needed to more definitively define the specific role of these genes in AVM pathogenesis. The authors also propose that these genes highlight the ability of endothelial cells of AVM to lose their arterial/venous specificity and acquire a partial lymphatic molecular phenotype[37]. The significance of these findings is that these markers may help clinicians to predict hemorrhage risk, given their association with inflammatory and hemorrhagic processes at the molecular level.

In understanding the genetic basis of AVM development, it is also important to discuss our genetic understanding of the vascular stability of these lesions. Deficient expression of platelet-derived growth factor subunit B (*PDGFB*) and its linked *PDGF* receptor beta can result in weakened vessels due to deficient pericyte recruitment and vascularization (Figure 2)[9,16]. Pericytes are multifunctional mural cells that play a role in the regulation of brain angiogenesis, blood-brain barrier (BBB) integrity, and vascular stability[38]. Reduced pericyte migration in bAVM can also result in increased rate of blood flow through the lesion and therefore increased risk for microhemorrhages in unruptured bAVM[38]. In addition, Shaligram *et al.* reported that the dysregulation of angiopoietin-1 and angiopoietin-2 results in increased BBB permeability and risk for bAVM rupture[9]. In addition, it has been reported that 30% of bAVM overexpress angiopoietin-2, signifying the need to further explore its role in bAVM[39].

The role of non-coding RNAs in AVM pathogenesis has also gained increased attention in the literature. Chen *et al.* identified three critical microRNAs (miRNAs) involved in VEGF

signaling in blood samples of patients with bAVM compared to healthy controls: miR-7–5p, miR-199a-5p, and miR-200b-3p[40]. Therapeutic approaches to targeting *VEGF* via the use of small interfering RNAs have also been reported[41]. Identification of these miRNA can provide insight on the role of these noncoding aspects in bAVM pathogenesis and future studies are warranted.

3.3. Epigenetic mechanisms in AVM formation

Understanding the epigenetic landscape is also important to decipher the formation and growth of AVM lesion. Transcriptional and metabolite level changes have been shown to play a role in the angiogenesis of AVM[34]. Elucidating these epigenetic signals has been approached by several authors. DNA methylation in vascular development has been shown to impact the atherogenesis process at the endothelial cell level[42]. Chan *et al.* reported that promoter DNA methylation plays an important role in the cell-specific expression of the constitutively expressed endothelial nitric-oxide synthase (*eNOS*) gene in the vascular endothelium[43]. Rao *et al.* proposed that methyl-CpG-binding domain protein 2 (*MBD2*), an interpreter for DNA methylome-encoded information, could be a worthwhile epigenetic target for modifying endothelial function because of its associated role in VEGF signaling[44].

Variations in histone modifications have also been implicated in AVM pathogenesis. Histone acetylation has been shown to be impacted by hemodynamic forces and blood flow through enzymatic changes of histone acetyl transferases (HATs)[45]. Lee *et al.* showed that HDAC molecules play a regulatory role in oxidative, inflammatory, and proliferative responses of endothelial cells in response to disturbed flow with oscillatory shear stress[46]. These changes in blood flow result in post-translational modifications in chromatin structure[46]. The role of histone deacetylase 7 (*HDAC7*) functioning has also been implicated in angiogenesis, and its downregulation results in impaired vascular growth[47].

The current breadth of literature elucidating the genetic mechanisms at play and their impact on the signaling pathways in bAVM formation provides an opportunity for the future therapeutic options. Next, we provide a summary of the most supported candidate genes associated with AVM.

4. Candidate genes involved in AVM formation

Several candidate genes have been implicated in the development of AVM for their involvement in the regulation of blood vessel formation, signaling pathways, and cell proliferation.

Mitogen activated protein kinase kinase 1 (*MAP2K1*) is the gene that codes for MAP-extracellular signal-regulated kinase 1 (*MEK1*). This gene produces a protein that belongs to the family of dual specificity protein kinases and functions as a mitogen-activated protein kinase. MAP kinases serve as an integration point for many biochemical signals. This kinase, located upstream of MAP kinases, activates their enzymatic activity in response to various intracellular and extracellular signals. It is involved in numerous cellular activities, including proliferation, differentiation, determination, transcription control, apoptosis, and

development[48,49]. It is a crucial part of the MAP kinase signal transduction pathway. Studies have shown that most sporadic extracranial AVM has an endothelial cell-specific *MAP2K1* mutation[50,51]. More specifically, the most common mutation associated with AVM is *MAP2K1-K57N*, and it over-activates the RAS/MPK pathway in endothelial cells[51]. It has been hypothesized that the aberrant coordination of artery-capillary-vein development may result from the activation of RAS/MAPK signaling by mutant endothelial cells. *MAP2K1* mutant endothelial cells that interfere with normal vascular development may result in abnormal attachment of arteries and veins[51].

The RAS P21 protein activator 1 (*RASA1*) gene produces a cytoplasmic protein that belongs to the GAP1 family of GTPase-activating proteins. Furthermore, *RASA1* regulates Ras GDP and GTP and is involved in a myriad of physiologic processes, such as angiogenesis, cell proliferation, and apoptosis. The gene product increases the GTPase activity of normal RAS p21. The protein acts as a suppressor of RAS function by boosting the RAS proteins' poor intrinsic GTPase activity, which results in the inactive GDP-bound form of RAS and permits control over cellular proliferation and differentiation[52]. Heterozygous mutation of the *RASA1* gene causes capillary malformation AVM (CM-AVM) 1 disorder[53]. Hongo *et al*. states that the majority of inherited *RASA1* mutations in CM-AVM1 are nonsense, frameshift, or splice-site mutations[54]. Some studies have also shown that complete inactivation of *RASA1* may arise because of a second-hit somatic mutation in endothelial cells[54,55].

Numerous developmental processes, particularly those involving the nervous system, are mediated by ephrin receptors and their ligands, the ephrins. The largest subset of the receptor tyrosine kinase (*RTK*) family is ephrin receptors[56]. The ephrin-A (EFNA) class, which is tethered to the membrane by a glycosylphosphatidylinositol bond, and the ephrin-B (EFNB) class, which are transmembrane proteins, are separated from one another based on their structures and sequence correlations[57]. In addition to being important axon guidance regulators during nervous system development, erythropoietin-producing hepatocellular (Eph) receptor tyrosine kinase receptors and their ligands, ephrins, also play a significant role in many aspects of blood vessel morphogenesis[58]. Approximately half of the patients with CM-AVM exhibit heterozygous mutations in the *RASA1* gene. The *EPHB4* gene is the second gene mutated in patients with CM-AVM that does not exhibit any mutations in the *RASA1* gene[56]. CM-AVM resulting from mutated *EPHB4* and *RASA1* genes is characterized by small multifocal capillary malformations (CM) and increased risk for fast-flow vascular malformations, but clinical features differ, and CM-AVM2 is inherited as an autosomal-dominant disorder[52].

Choi *et al*. used mouse models to show that homozygous deletion of *ENG* in endothelial cells is vital for the development of HHT Type 1 (HHT1) brain with AVM phenotype[59]. Activin-like kinase 1(*ALK-1* or *ACVLR1*) is a transmembrane kinase that encodes TGF-β Type 1 receptor and its proteins are also expressed on endothelial cells[60]. Loss-of-function mutation in *ACVRL1* leads to dysregulation of TGF-β/BMP signaling, which would negatively impact proliferation, migration, and recruitment of cells[54]. Kim *et al*. stated that *BMP-9* may be a physiologically significant endothelial signaling channel for HHT development, according to studies that reveal that ALK-1 may instead signal through it

and that endoglin can strengthen the signal[30]. Although only contributing < 1% to HHT etiology, mutations in an additional causative gene called growth differentiation factor 2 (*GDF2*) can cause rare vascular abnormality syndromes that resemble HHT[61]. Assorted studies have reported missense, homozygous, and in some cases, a complete deletion of the entire *GDF2* region in people with HHT[62–64]. Another causative gene for AVM pathogenesis in relation to HHT is the *SMAD4* gene, which encodes the downstream effector for both TGF-β and BMP signaling[30]. *SMAD4* mutations include missense, non-sense, and frameshift mutations and they cause juvenile polyposis HHT (JP-HHT) in patients[65,66].

KRAS mutations were found in endothelial cell-enriched cultures obtained from sporadic brain AVMs[67,68]. Nikolaev *et al*. found that *in vitro* activation of mutant KRAS in endothelial cells increased extracellular signal-regulated kinase (*ERK*) activity, angiogenesis and Notch signaling gene expression, and enhanced migratory behavior[68]. More precisely, bAVM can be caused by endothelial-specific gain-of-function mutations in *KRAS* (G12D or G12V), as demonstrated in mice and zebrafish by Fish *et al*.[69] Although studies have shown that constitutive activation of the MAPK/MEK/ERK signaling pathway by somatic mutations in the *KRAS* gene is the most known cause of sporadic brain AVM, the mechanism is still poorly understood[68–73]. Active *KRAS* signaling caused ectopic sprouting, increased arterial lumen diameter, altered endothelial cell morphogenesis, increased cell size, and direct linkages between arteries and veins[69]. As one of the RAF proteins, BRAF (encoded by *BRAF* gene) also activates the RAF/MEK/ERK (MAPK/ERK) signaling pathway[54]. These pathways regulate crucial cellular growth, survival, and senescence[74]. Bameri *et al*. showed that there was significant prevalence of *BRAF* mutations in bAVM, which were however less common than *KRAS* mutations[33].

Many AVM is sporadic and SNPs in some specific genes have been shown to be responsible for the sporadic susceptibility to bAVM[75]. SNPs in the following genes: *IL-6*, *IL-1*, *IL-1*β, tumor necrosis factor (*TNF*), transforming growth factor-beta 2 (*TGFRB2*), matrix metallopeptidase 3 (*MMP3*), angiopoietin like 4 (*ANGPTL4*), and *VEGFA* have been linked to bAVM with *IL-6*, *TNF* and activin receptor-like kinase-1 (*ACVRL1*) being the most frequently linked[54,76,77]. SNPs in these genes increase the inflammatory response to provocation and result in an overabundance of pro-inflammatory cytokines, which in turn exacerbates the inflammatory response, recruits leukocytes, and activates the endothelial cells of the AVM[76]. This eventually leads to increased vascular injury and angiogenesis, which result in the formation and expansion of AVM[76,78]. Li *et al*. showed that *de novo* germline mutations in genes including endoglin (*ENG*), junction plakoglobin (*JUP*), exophilin 5 (*EXPH5*), and endothelial PAS domain-containing protein 1 (*EPAS1*) were found to be potentially related to sporadic bAVM pathogenesis in a study that performed whole exome sequencing of case-unaffected-parental bAVM trios (Table 1)[79].

5. Genetic considerations of AVM and rupture

The most devastating clinical outcome of AVM occurs secondary to bAVM rupture resulting in intracerebral hemorrhage. There are several genetic factors that have been explored and reported in the literature to be associated with increased risk of bAVM rupture in patients.

Estimating the risk of ICH and determining the costs and benefits of intervention tend to be a challenge when managing bAVM. Pawlikowska *et al.* demonstrated that polymorphism in *IL-6* could be linked to ICH in bAVM[80]. According to Pawlikowska *et al.*, bAVM patients homozygous for the *IL-6*–174G allele (GG genotype) had a greater risk of presenting with ICH (OR [odds ratio], 2.62, *P*=0.003) than IL-6–174C carriers[80].

The support for *IL-6* as a genetic risk factor has been further reiterated with primary research data. Chen *et al.* also demonstrated that the GG genotype of *IL-6* was also associated 57with increased gene expression of *IL-6* compared to the GC and CC genotypes. This homozygous genotype was associated with increased risk of hemorrhage[81]. The clinical utility of these findings demonstrates that diagnostic genotyping in patients with bAVM for *IL*-6 could be useful in determining the need for a patient to have early surgical intervention or other preventative therapeutic options. The correlation between increased IL-6 protein in bAVM tissue postoperatively and risk of hemorrhage in bAVM stems from the increased expression of MMP in bAVM[81]. MMPs are known to be involved in vascular remodeling, adaption, and repair[81]. In animal models, it was found that *IL-6* activated and induced expression of MMP-3 and MMP-9, and subsequently increased proliferation and migration of cultured human cerebral endothelial cells[81]. Therefore, increased levels of IL-6 in humans may be involved in the upstream regulation of MMP-3 and MMP-9, which would lead to instability of the blood vessels[81]. Furthermore, *IL6* expression may modulate downstream inflammatory and angiogenic targets that result in ICH. Thus, our genetic understanding of *IL6* and its protein products and their involvement in bAVM growth and eventual ICH rupture can provide essential clinical information, which can aid in diagnostic testing and risk stratification.

SNPs in *TNF*-α and apolipoprotein E (*APOE*) have also been associated with AVM rupture. Kim *et al.* reported TNF-α as a genetic risk factor for AVM rupture[30]. In a cohort of 280 patients with AVM, the A allele of the *TNF*-α–238G > A promoter SNP was associated with new hemorrhage[30]. They reported an HR of 4.0 (95% CI = 1.3 – 12.3; $p = 0.015$) with adjustment of initial presentation with hemorrhage, age and race/ethnicity. Pawlikowska *et al.* reported on APOE ε2, but not APOEε4 allele, being associated with new hemorrhage ($n = 284$) in the natural course of AVM cases, with an adjusted HR of 5.1 (95% CI = 1.5 – 17.7; $p = 0.01$)[82]. In addition, both APOEε2 and TNF-α–238 A alleles were independent predictors of ICH risk in a multivariate model[82]. In addition, they also appear to confer greater risk for post-radiosurgical and post-surgical hemorrhage[30].

Our knowledge of the genetic risk factors associated with AVM and their rupture has continued to garner research interest due to its clinical utility. Future studies to continue validation of these risk factors will require large clinical datasets and continued replicative studies. In addition, taking into consideration a patient's genomic makeup and contributory epigenetic and clinical risk factors would altogether provide a more accurate estimation of risk of AVM rupture to modulate its potential devastating outcomes.

6. Genetic conditions associated with AVM

While our discussion thus far has focused on cerebral AVM and their clinical outcomes, it is also imperative to note that AVM is present in several other genetic syndromes which we have mentioned but they will be highlighted in more detail in this section.

6.1. HHT

HHT, also known as Osler-Rendu-Weber syndrome 1, is an autosomal dominant vascular dysplasia consisting of epistaxis, mucocutaneous telangiectasias, and AVM, affecting one in 5000–8000 individuals[26,54]. HHT is a clinical diagnosis marked by the presence of at least three of the following features per the Curacao criteria: Multiple mucocutaneous telangiectasias, recurrent epistaxis, visceral organ AVM, and HHT diagnosed in a first-degree relative[54,83]. These features demonstrate age-related penetrance with 50% of individuals developing epistaxis by age 10, and 80–90% by age 21. Moreover, telangiectasias arise in nearly all patients by late adulthood[54]. In addition to the brain, HHT commonly presents with AVM in the liver and lungs[54,84].

Loss-of-function mutations in *ENG*, *ACRVL1* or *ALK1*, and *SMAD4* have each been identified as the cause of a particular subclass of HHT[26,54]. HHT is subdivided into two main subtypes; HHT1 and HHT2. The classification of these subtypes is dependent on loss-of-function mutations in two genes connected to TGF signaling pathways. For instance, loss-of-function mutation in *ENG*, which codes for an accessory protein in the TGF-B receptor complex, is linked to HHT-1, while loss-of-function mutation in *ACVLR1*, a gene that codes for a transmembrane kinase associated with TGF-B signaling, causes HHT-2[26]. Interestingly, *ACVLR1* has also been associated with signaling through the BMP-9, and ENG was shown to potentiate that signal. Therefore, aberrations in the BMP-9 endothelial signaling pathway have been postulated to contribute to HHT pathogenesis[26].

Clinically, both HHT-1 and HHT-2 share all the classic manifestations of HHT, such as epistaxis, telangiectasias, and visceral AVM; however, the occurrence of bAVM is approximately 10 higher in HHT-1 compared to HHT-2[54,85,86]. Approximately 10% of patients with HHT have bAVM[26,87]. Over 40% of patients with HHT develop multiple bAVM with 50% manifesting symptoms, and occurrence of rupture occurs in 20% of patients. While they cannot be distinguished solely on the basis of their angioarchitecture, each have distinctive features. For example, compared to the sporadic form of bAVM, those associated with HHT are smaller with an average nidus of < 3 cm (about 1.18 inch), while the average nidus in sporadic bAVM is approximately 3 cm[54,85]. Loss-of-function mutations in *ENG* confers a 1000-fold increased risk of developing bAVM compared to sporadic lesions, whereas loss-of-function mutations in *ACVLR1* increase the risk by 100 folds[26].

Additional genetic risk factors for AVM have been identified, namely, SNPs in *TNF*-α and *APOE*, which are associated with downstream vascular derangements. Kim *et al.* report that the A allele of the *TNF*-α–238G > A promoter SNP was associated with new hemorrhage in the natural course of a sample of 280 AVM cases.

6.2. CM-AVM

Capillary malformation-AVM (CM-AVM) is an autosomal dominant vascular syndrome characterized by small, multifocal vascular macules with or without fast-flow vascular lesions[54,88,89]. Typical fast-flow lesions include arteriovenous fistulas and AVM predominantly in the central nervous system, head and neck, and/or limbs[54,89–91]. These macules typically are reddish-brown to pink with peripheral halos, although these colors change and become browner with age[53,54,90]. While it has been reported that these macules represent capillary malformations, histopathologic and ultrasonic examinations have confirmed that they are in fact cutaneous micro or incipient AVM[54,90,91]. The macules of CM-AVM can be distinguished from other disorders such as simple cutaneous capillary malformations by the presence of the peripheral halos. This pale rim is postulated to be the result of the AVM siphoning blood from the tissue immediately surrounding it, which reduces blood flow to the area[91]. Approximately one-third of patients with CM-AVM present with fast-flow vascular lesions in the CNS or skin with 10% occurring in the brain[54,88,90,92].

The most common cause of CM-AVM is loss-of-function mutations in the *RASA1* and *EPHB4* genes with a penetrance of 89–95%[41,54]. Similar to HTT, CM-AVM can also be subdivided based on which gene has been mutated. CM-AVM1 is caused by a heterozygous loss-of-function mutation in the *RASA1* gene[41,54]. *RASA1* encodes RASp21, which is a protein that acts as a suppressor of RAS function by boosting the RAS proteins' poor intrinsic GTPase activity, which results in the inactive GDP-bound form of RAS and permits control over cellular proliferation and differentiation[93]. Typically, the inherited mutation is non-sense, frameshift, or a splice-site mutation resulting in a premature stop codon[54,92,94]. Conversely, loss-of-function mutation of the *EPHB4* gene results in CM-AVM2 variant[54,61,95]. *EPHB4* encodes EphB4, a tyrosine kinase receptor that, along with its ligand, ephrinB2, is a key mediator in angiogenesis[96,97]. Contrary to CM-AVM1, 50% of the mutations associated with *EPHB4* are loss-of-function mutations associated with null alleles, while the remaining 50% are missense mutations[54,95,98]. These missense mutations typically affect the extracellular domain or the intracellular protein tyrosine kinase domain[54,95]. Clinically, CM-AVM1 and CM-AVM2 have similar presentations. However, fast-flow vascular malformations are typically associated less with CM-AVM2 compared to CM-AVM1. Of patients with CM-AVM2, an estimated 18% present with fast-flow vascular malformations, of which only 3% occur in the brain[54,95].

6.3. Parkes Weber syndrome and Sturge Weber syndrome

Parkes Weber syndrome (PWS) is characterized by a triad of limb hypertrophy, port-wine stain, and high-flow AVM[99,100]. PWS is a congenital vascular disorder associated with mutations in *RASA1*[100,101]. The prevalence of this condition is not well described, and it does not appear to have a predilection for race or gender. The most severe feature of this disease is the high-flow AVM that commonly cause secondary symptoms, such as venous hypertension, pain, limb fatigue, and high-output heart failure[100]. One systematic review on the clinical, diagnostic, and treatment modalities of PWS concluded that a diagnosis of PWS should be made based on the presence of capillary, venous, lymphatic malformation,

and AVM in an overgrowth extremity. However, it is the latter finding—that is, the presence of high-flow AVM — that distinguishes PWS from other congenital vascular disorders[101].

Sturge Weber syndrome (SWS) is a sporadic neurocutaneous congenital disorder that affects one in 20,000 to 50,000 live births[83–85]. Although SWS is mostly caused by somatic activating R183Q GNAQ mutations, emerging evidence has implicated somatic mutations in GNA11 and GNB2 in the pathogenesis of SWS[85]. SWS is associated abnormal vasculature in the brain, skin, and eye resulting in characteristic facial capillary malformations (port wine stain), glaucoma, and leptomeningeal angiomatosis[83–85]. The leptomeningeal angiomatosis is characterized by an increased number of capillaries with a reduced number and size of veins in the pia mater and cerebral cortical surface. While rare, bAVM has been reported with SWS, occurring primarily among infants[83,86–88]. The underlying mechanism of bAVM in SWS remains unknown, but it has been posited that the vessel malformation occurring in such cases happens at a different stage than would otherwise occur in classic SWS[83].

In the realm of precision medicine, a thorough foundation of genetic basis for disease can prove especially useful for more innovative treatment approaches. Next, we discuss the ongoing research on and the emerging treatment options for AVM both in its sporadic form and its associated genetic conditions as well as the impact of varying genotypes and its related targeted therapies (Table 2).

7. New advances and emerging treatments

The management of AVM typically calls for a multidisciplinary approach. New and emerging treatments for AVM have been developed due to recent developments in the field of study. This section will discuss some of the most exciting recent discoveries and cutting-edge AVM therapies. Due to the risk and controversies associated with surgical, endovascular, and radiotherapeutic procedures, there has been an increase in the demand for pharmacological treatment modalities. Pharmacological therapies targeting various critical mediators involved in AVM formation at the genetic level are effective.

Bevacizumab is a humanized monoclonal antibody shown in numerous clinical studies as an anti-angiogenic therapy for HHT patients due to its ability to bind and neutralize human VEGF (Figure 3)[89–91]. VEGF has been shown to be implicated in the formation of bAVM as discussed previously[54,92]. Robert *et al.* reported that bevacizumab has been enrolled in an ongoing phase III randomized clinical trial involving HHT patients (NCT03227263)[41]. Zhu *et al.* also showed that adeno-associated virus-mediated expression of soluble FMS-related tyrosine kinase 1 (sFLT-1) can reduce bAVM severity by inhibiting VEGF-dependent downstream signals[93].

Using angiopoietin-2 (ANGPT2) monoclonal antibodies, Crist *et al.* proved successful alleviation and prevention of AVM formation in *Smad4*-deficient mice through inhibition of downstream ANGPT2, which is an antagonistic ligand of TEK (receptor tyrosine kinase) in the angiopoietin-TEK signaling pathway[94]. Ola *et al.* also showed that the inhibition of

the PI3K via PI3-kinase inhibitors in the PI3K-AKT signaling pathway reverses established AVM in *Alk1*-deficient mice models[95].

Disruption of signaling pathways of genes, such as *SMAD4*, *ALK1*, and *ENG*, as a result of loss-of-function mutations, is causes of HHT[54,96,97]. Tacrolimus and sirolimus, two immunosuppressive medications, have been discovered to activate pathways downregulated in forming AVM, suggesting possible therapies for HHT[98,99]. Tacrolimus is a potent stimulator of Smad1/5/8 signaling in cell and *Alk1*-deficient mice. Tacrolimus treatment also alleviated HHT vascular disease in mice and addressed the signaling and gene expression abnormalities brought on by endothelium *Alk1* suppression[98]. Sirolimus uses the PI3K-Akt-mTOR cascade to inhibit the overactivation of mTOR in patients with HHT. Sirolimus and nintedanib (tyrosine kinase inhibitor) function synergistically to normalize the Smad1/5/8, mTOR, and VEGFR2 pathways and effectively reverse AVM formation in the retina of *Bmp9*-immunodeficient mice[99].

Zhu *et al*. showed that thalidomide and lenalidomide (safer derivative with similar efficacy) treatment in *Alk1*-deficient mice not only reduced inflammation and hemorrhage in established bAVM but also inhibited the development of bAVM via the upregulation of the platelet-derived growth factor B (PDGFB) and platelet-derived growth factor receptor-β (PDGFR-β) signaling pathway[102]. Although the role of PDGFB/PDGFRβ signaling in human bAVM pathogenesis is mainly unknown, expression of *PDGFR*β was reduced in bAVM[103]. Somatic activating mutations in the *KRAS* gene cause excessive activation of the MAPK-ERK pathway in endothelial cells, occasionally leading to sporadic AVM[67,68]. Inhibiting the MAPK-ERK cascade with MAP-ERK kinase inhibitors may be a promising approach to treating non-hereditary bAVM because higher levels of *ERK* expression were seen in cells with the mutant KRAS protein. Al-Samkari *et al*. reported on phase II trials (NCT04258046 and NCT05125471) in the United States and EudraCT 2019-003573-26 in Europe that evaluate the use of trametinib (MEK inhibitor) in AVM[100]. Nicholson *et al*. also reported a case study in which a patient with CM-AVM was successfully treated with trametinib[101].

Despite advancements in pharmaceutical therapies that inhibit AVM formation and progression, open microsurgical AVM excision is still the most efficient treatment for bAVM. Pharmacologic therapies are being developed as adjuncts to surgical resection or to minimize AVM size and symptoms in individuals with high-grade AVM and elevated surgical risks. In the future, customized genomic medicine may be used as a therapeutic strategy when we have a better grasp of the genetic abnormalities and signaling pathways connected to the development of bAVM. Thus, locating active gene mutations and using inhibitors to target their signaling pathways are fundamental to personalized AVM treatment.

8. Options for testing SNPs

Genetic testing plays a key role in diagnosing and managing AVM, particularly in patients with HHT, a genetic disorder that predisposes individuals to AVMs[104]. In this section, we discuss the potential innovative testing options for SNPs analysis in saliva and microRNA analysis in blood for specific genes associated with AVM. Genetic testing for AVM can

be performed using various methods, including NGS, polymerase chain reaction (PCR), and microarray analysis. NGS is a powerful tool that enables the sequencing of the entire genome or specific genes of interest, facilitating the identification of novel genetic variants associated with AVM[105]. On the other hand, PCR is a widely used method for detecting specific genetic mutations in AVM-related genes, such as *ENG*, *ACVRL1*, and *SMAD4*, which are commonly mutated in HHT[106]. In addition, microarray analysis can detect AVM-related genetic variations, including copy number variations and SNPs.

Pawlikowska *et al*. genotyped 180 patients with bAVMs and found that the risk of hemorrhagic presentation was 3-fold higher in those carrying the −174GG genotype of the *IL-6* gene, compared with subjects carrying the CC and GC genotypes[80,107]. Achrol *et al*. tested the association between two SNPs in the promoter region of the *IL-6* gene (–174G > C and −572G > C) and two SNPs of the tumor necrosis factor alpha (*TNF*α) gene (–238G > A and −308G > A) with the risk of new ICH after diagnosis in 280 patients with bAVMs[108]. The −238G > A polymorphism of the *TNF*α gene was associated with an increased risk of bleeding during the natural course of the disease. Similarly, Kim *et al*. found that the same polymorphism (–174G > C) of the *IL-6* gene was associated with a 2-fold increased risk of bAVM susceptibility among Latinos after accounting for differences in ancestral background[109]. Other SNPs that have been associated with AVM and ICH include the −31T>C and −511C>T polymorphisms of the *IL-1*β gene, the −197G>A polymorphism of the *IL-17A* gene, and the −707A>G polymorphism of the *MMP-3* gene[110–112]. These SNPs can be tested for using innovative testing options for SNPs in saliva and microRNA analysis in blood. These non-invasive testing options offer several advantages over traditional methods of genotyping SNPs, including reduced patient discomfort, lower costs, and faster turnaround times.

Saliva-based testing has emerged as a promising and non-invasive approach to genetic analysis[113]. Saliva samples contain DNA that can be extracted and analyzed for genetic variations associated with AVM. SNPs, which are single nucleotide changes in the DNA sequence that can affect gene expression and protein function, are commonly detected using saliva-based testing[114]. Saliva-based testing for SNPs associated with AVM can provide valuable information on diagnosis, prognosis, and treatment, allowing for personalized approaches to patient care.

MicroRNA analysis through blood is another innovative testing option for specific genes associated with AVM. MicroRNAs are small non-coding RNA molecules that regulate gene expression by binding to messenger RNA (mRNA) and inhibiting translation. Studies have shown that miRNAs play a critical role in the development and progression of AVM[115]. Analyzing miRNA expression patterns in blood samples can provide insights into the regulatory mechanisms and potential biomarkers involved in AVM. Specific miRNAs may exhibit altered expression levels in individuals with AVM, indicating their potential role in disease pathophysiology. Identifying miRNAs associated with AVM can enhance our understanding of the condition’s molecular mechanisms and potentially lead to the development of novel diagnostic and therapeutic strategies[116].

Taken together, genetic testing is essential for diagnosing and managing AVM, especially in patients with HHT. Innovative testing options, such as SNP analysis through saliva and miRNA analysis through blood, offer non-invasive and convenient approaches for diagnosing, predicting, and treating AVM. Further research is needed to validate the clinical utility of these testing options and uncover novel genetic variants associated with AVM.

9. Conclusion

Our understanding of the genetics mechanisms at play in bAVM pathogenesis and growth has continued to expand over the past decade. Several genes and their downstream protein products have been implicated in the angiogenesis and pathological formation of AVM. These discoveries have largely helped elucidate the role of signaling proteins, which may also affect the vascular stability bAVM and ultimately result in their downstream rupture and more devastating clinical consequences. As we have presented, there are a slew of genes that have been in implicated in bAVM formation. Notably, *KRAS* and *IL6* have significance in sporadic bAVM phenotype. We also presented in detail the role of these genetic alteration in signaling pathways and targets for endothelial cellular proliferation, migration, and angiogenesis. The emerging treatment paradigms of AVM help stratify patient risk for downstream clinical consequences such as intracerebral hemorrhage, seizures, and neurological deficits. However, much remains to be understood about the mechanisms at play in bAVM formation. The research community has explored the use of genetic testing to evaluate interventional strategies. Further studies are needed to identify genetic polymorphisms, which are associated with bAVM and its clinical manifestations. With further studies, the exploitation of these genetic targets will hopefully result in successful improved clinical management strategies, novel therapeutic approaches, and more personalized care.

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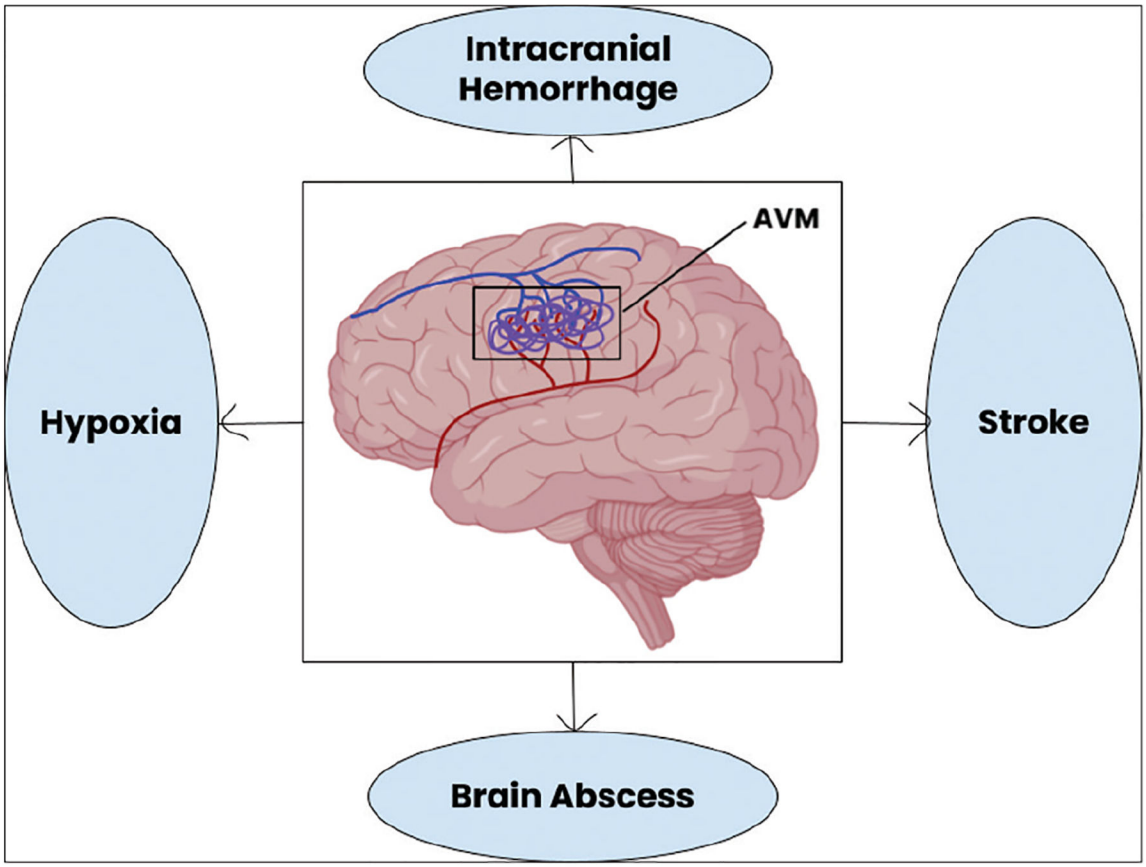

Figure 1.

Clinical consequences of AVM rupture. AVM is defined as vascular shunts connecting arteries and veins. Common consequences of AVM rupture in the brain include hypoxia, stroke, ICH, and abscess.

Abbreviations: AVM: Arteriovenous malformations, ICH: Intracranial hemorrhage.

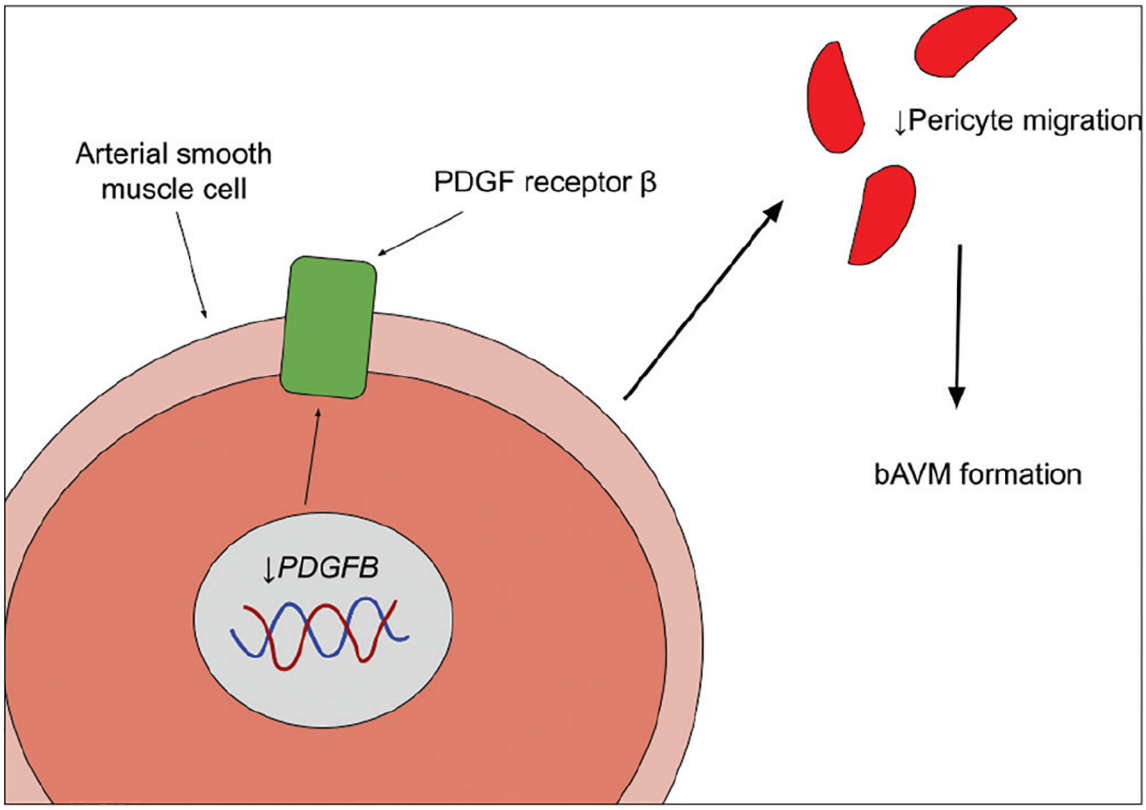

Figure 2.

The role of PDGFB in bAVM pathogenesis. Schematic of hypothesized relationship between decreased expression of *PDGFB* and bAVM. Pericytes are thought to be key mediators in this pathway. Decreased expression of *PDGFB* results in aberrant *PDGFB* signaling and resultant deficient pericyte recruitment and vascularization and eventual bAVM formation. Abbreviations: PDGFB: Platelet-derived growth factor subunit B; bAVM: Arteriovenous malformations of the brain.

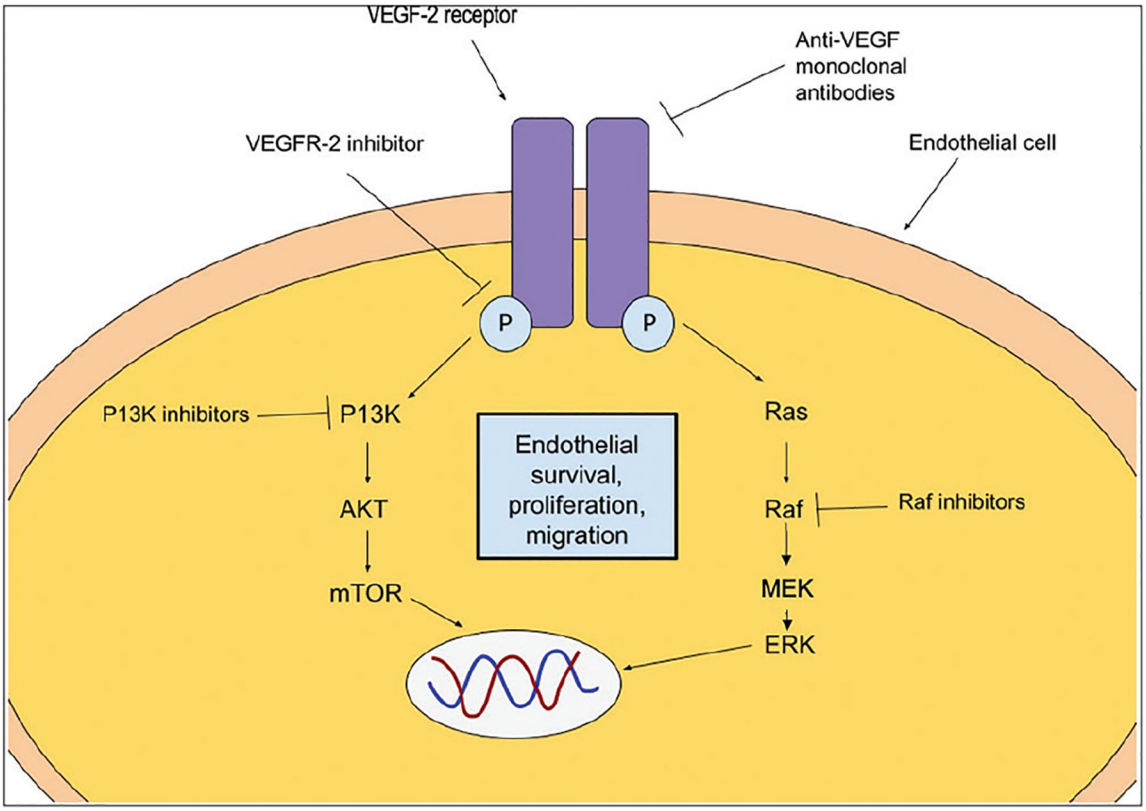

Figure 3.

VEGF as a therapeutic target. The VEGF receptor, which is intimately involved in endothelial proliferation, is a key target for emerging interventions.

Abbreviation: VEGF: Vascular endothelial growth factor.

Table 1.

Top candidate genes associated with AVM development and pathogenesis

References	Genes	Mutations and their impacts
Couto *et al.*[50]	*MAP2K1*	Gain-of-function mutation, MAP2K1-K57N; activates RAS/MPK signaling
Revencu *et al.*[52]	*RASA1*	Activates RAS GTPase
Amyere *et al.*[96]	*EPHB4*	Loss-of-function mutation; dysregulates vascular development and causes vascular defects
Fish *et al.*[69]	*KRAS*	Gain-of-function mutation; involved in constitutive MAPK/MEK/ERK signaling
Hongo *et al.*[54]	*ALK-1*	Loss-of-function mutation; dysregulates TGF-β/BMP signaling
Sturiale *et al.*[77]	*IL-6* *IL-1* *IL-1β*	Contributes to inflammatory processes, including leukocyte recruitment and endothelial activation
Hongo *et al.*[54]	*BRAF*	Activates RAF/MEK/ERK (MAPK/ERK) signaling

Abbreviations: IL: Interleukin; AVM: Arteriovenous malformations; TGF-β: Transforming growth factor beta 1; BMP: Bone morphogenetic protein.

Table 2.

An overview of syndrome associated with AVM, inheritance pattern, and associated genes

Conditions	Inheritance pattern	Common associated genes
HHT	Autosomal dominant	*Endoglin, ACVRL1*
Capillary malformation-arteriovenous malformation	Autosomal dominant	*RASA1, EPHB4*
Lymphatic malformation	Sporadic	*PIK3CA, AKT1*
Sturge Weber syndrome	Sporadic	*GNAQ*
Parkes Weber syndrome	Autosomal dominant	*RASA1*

Abbreviations: AVM: Arteriovenous malformations; HHT: Hereditary hemorrhagic telangiectasia.