

Molecular-genetic mechanisms of cerebral arteriovenous malformations: a systematic review of germline, somatic and experimental evidence

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Systematic Review

Keywords: Cerebral arteriovenous malformation, KRAS, Somatic mutation, Hereditary hemorrhagic telangiectasia, MAPK signaling, Systematic review

Posted Date: September 10th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9966668/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background. Cerebral arteriovenous malformations (AVMs) are high-flow vascular anomalies that carry a considerable burden of haemorrhagic morbidity. Work over the past decade has shown that both inherited syndromes and apparently sporadic lesions can be traced to alterations in a handful of signalling pathways, but the relevant evidence sits awkwardly between human genetic studies, animal models, and molecular profiling experiments.

Objective. To bring together the current evidence on the molecular and genetic underpinnings of cerebral AVM formation, clinical course, and candidate therapeutic targets.

Methods. We searched MEDLINE (PubMed), Embase, Web of Science Core Collection, and Scopus from inception to 1 January 2026. Records were screened, and full texts assessed, by two reviewers working independently. Studies were eligible if they reported genetic, molecular, or epigenetic data on cerebral AVMs. Because of substantial heterogeneity in designs and outcomes, evidence was synthesised qualitatively.

Results. Of 343 records, 44 primary studies (28 clinico-genetic and 16 experimental) together with 20 reviews and meta-analyses met inclusion. Inherited AVM syndromes largely reflected germline variants in the TGF- β /BMP network (ENG, ACVRL1, SMAD4, GDF2/BMP9) or in arteriovenous-specification regulators (RASA1, EPHB4); penetrance was incomplete and there was support for local modifying "second-hit" events. Resected sporadic cerebral AVMs often carried somatic activating mutations in the RAS/MAPK cascade—mostly KRAS, less often BRAF—at low variant allele fractions that demanded high-sensitivity assays. Endothelial-specific activation of KRAS or BRAF reproduced AVM-like phenotypes in vivo and showed MEK–ERK dependence. Susceptibility variants (notably at 9p21/ANRIL), inflammatory mediators, extracellular-matrix remodelling, and epigenetic changes appear to fine-tune lesion behaviour and haemorrhagic risk.

Conclusions. Syndromic predisposition and clonal somatic events in endothelium converge on a small set of developmental signalling axes that govern angiogenesis and vessel-wall maturation. Diagnostics anchored in this biology, together with pathway-targeted therapy, now need prospective evaluation, paired with standardised approaches for detecting low-level mosaicism.

Introduction

Brain arteriovenous malformations (bAVMs) are vascular anomalies in which arteries shunt directly into veins, without an intervening capillary bed, producing a high-flow lesion. The chronic haemodynamic stress that follows reshapes the vessel wall and raises the risk of rupture [2–4].

Reported prevalence is roughly 10–18 per 100,000, with an annual incidence of about 1 per 100,000 [2–4]. Most patients present in young or middle adult life, with mean age at diagnosis in the 34–47 year range [4, 73]. The dominant clinical concern is intracerebral haemorrhage, which is the first manifestation in roughly 45–50% of patients; the annual rupture risk sits at 2–4% [2, 4, 27]. Unruptured lesions can also declare themselves through seizures, chronic headache, or focal neurological deficits [17].

Cerebral AVMs were long regarded as essentially sporadic, but familial clusters and well-defined syndromic forms now point to a sizeable genetic contribution [19, 44, 52, 91]. The best-characterised example is hereditary haemorrhagic telangiectasia (HHT; Rendu–Osler–Weber disease), an autosomal-dominant condition caused by germline variants in the TGF- β /BMP pathway—most often in ENG (HHT1) and ACVRL1/ALK1 (HHT2), and less commonly in SMAD4 (juvenile polyposis–HHT) or GDF2/BMP9 [14–16, 18, 31, 37, 39, 44, 70, 80]. Disruption of this cascade compromises the control of angiogenesis, arteriovenous specification, and vessel-wall stabilisation.

A second well-defined group, the capillary malformation–arteriovenous malformation (CM-AVM) spectrum, includes congenital lesions and micro-AVMs linked to autosomal-dominant RASA1 and EPHB4 variants with incomplete penetrance [5, 19, 62, 63, 92]. The list of rare syndromes and individual variants tied to vascular malformations continues to grow, fitting comfortably within a multifactorial model.

Failure to find germline mutations in most apparently sporadic AVMs has long pointed to a role for postzygotic events in the vessel wall. Since the early 2010s, transcriptional profiling has shown that AVM endothelium loses much of its normal arterial/venous identity and takes on lymphatic-like features, with the Notch, VEGF, Wnt, and Hedgehog axes all implicated [66, 69, 82]. Activating KRAS mutations, mostly confined to the pathological endothelium, are by some distance the most frequently detected somatic alteration [7, 22, 24, 26, 33, 51, 59]; how specific variants map onto clinical severity remains unsettled [24, 59].

Alongside MAPK signalling, extracellular-matrix remodelling—driven by matrix metalloproteinases and chronic vessel-wall inflammation with raised IL-6, IL-8, and TNF- α —has also been implicated in AVM pathogenesis [1, 55, 68]. Epigenetic changes, including aberrant DNA methylation, dysregulated microRNAs, and altered chromatin states, appear to be part of the same picture [23, 30, 76, 77, 84].

Recent reviews have done justice to individual pathways—the KRAS/MAPK axis in sporadic lesions most prominently—but a synthesis that pulls together germline, somatic, epigenetic, and experimental evidence specifically for cerebral AVMs has been missing. We therefore set out to map the human and experimental evidence for germline and somatic mechanisms in cerebral AVMs, to appraise methodological quality, and to draw out what this means for molecular diagnostics and day-to-day neurosurgical practice.

Materials and Methods

The literature search ran across MEDLINE (via PubMed), Embase, Web of Science Core Collection, and Scopus from database inception to 1 January 2026. We supplemented this with backward and forward snowballing of reference lists from eligible primary studies. To mitigate the risk of confirmation bias, any supplementary targeted or gene-focused searches (including Google Scholar) were strictly limited to contextual mapping and reference tracing, and were not used as eligibility-determining searches. The review followed PRISMA 2020 [53, 54, 61, 78]; it was not prospectively registered in PROSPERO. Because we worked exclusively with previously published, anonymised aggregate data, neither ethical approval nor informed consent was required.

The core query, adapted to the syntax of each database, combined AVM and genetics terms: ((cerebral AVM OR cerebral arteriovenous malformation OR brain AVM OR brain arteriovenous malformation) AND (genetics OR genetic OR mutation OR somatic OR variant OR polymorphism* OR SNP OR GWAS)). We added refining terms (endothelium, signalling pathway, epigenetics, methylation, microRNA) and pathway- or gene-focused strings such as "KRAS mutation brain AVM", "BRAF V600E vascular", "ALK1 HHT brain", and "single-cell RNA sequencing AVM" where appropriate.

Eligibility criteria. Evidence was sorted into two tiers to avoid double counting. Systematic reviews and meta-analyses served as secondary contextual sources—useful for mapping the field and for reference snowballing—and were not counted as included primary studies. Primary inclusion required all of the following: (1) population—human cerebral or brain AVMs, or animal/cell models that explicitly modelled cerebral AVMs; (2) exposure—germline variants, somatic mutations, or transcriptomic/epigenetic changes; and (3) study type—cohort, case-control, case series, tissue sequencing, or experimental in vitro/in vivo work.

Exclusion criteria. Studies were excluded if they (1) provided no data on genetic, molecular, or epigenetic mechanisms relevant to cerebral AVMs; (2) addressed clinical management only, without mechanistic content; (3) had no accessible full text; (4) were duplicates (the most complete version was kept); (5) dealt exclusively with extracranial AVMs, vein of Galen malformations, cavernous malformations, or dural AV fistulas (unless cited strictly for comparative mechanistic context); or (6) were published in a language other than English or Russian.

Handling of indirect evidence. While the primary focus of this review was strictly on cerebral AVMs, we recognized that certain fundamental molecular mechanisms are shared across different anatomical locations of vascular malformations. Therefore, non-cerebral (extracranial) and spinal AVM models or cohorts were included in the qualitative synthesis only under the condition that no equivalent cerebral-specific data were available in the literature. In such cases, these non-cerebral studies were utilized exclusively to illustrate and extrapolate general molecular and pathogenetic mechanisms (e.g., shared MAPK pathway activation or TGF- β /BMP signaling defects).

Study selection (PRISMA). References were managed and de-duplicated in reference-management software, followed by two-stage screening. Title and abstract review, then full-text assessment, were undertaken independently by two reviewers; disagreements were settled by discussion, and where this failed, by a third reviewer.

The search returned 1005 records. After de-duplication, 1000 publications went forward to title/abstract screening, of which 910 were excluded for not addressing genetic or molecular aspects of AVMs. A total of 90 full-text articles were then assessed against the eligibility, including 20 secondary sources utilized for contextual referencing and snowballing. Ultimately, 44 primary studies met the inclusion criteria and were retained for qualitative synthesis. The PRISMA flow diagram (Fig. 1) summarises this process [53, 54, 61, 78].

Data extraction and synthesis. We built a comparative table of included primary studies (Table 1), capturing author/year, study design, sample size, genes analysed, type of genetic alteration, key findings, and methodology. A second table (Table 2) summarises the roles

of major genes and signalling pathways across the stages of vascular development. Two reviewers extracted data independently, with consensus resolving any discrepancies. Given the heterogeneity in designs, genetic-testing approaches, and outcomes, we opted for a qualitative (narrative) synthesis, organising findings by major molecular pathway and alteration type (germline vs somatic; SNP/GWAS; epigenetic), and flagging conflicting evidence where it arose.

Quality assessment and risk of bias. Methodological quality was appraised with tools selected for each study type: Q-Genie for genetic association studies, SYRCLE for animal work, and the JBI critical appraisal checklists for case series. For tissue sequencing studies, technical rigour was additionally judged on tissue source, endothelial enrichment, sequencing depth, and variant validation. To make the strength of inference explicit, we applied an evidence-tier framework: Tier 1 covered *in vivo* causal models and independently replicated tissue cohorts; Tier 2 single-cohort tissue sequencing and adequately powered candidate-gene associations; Tier 3 exploratory transcriptomic, epigenetic, and small-cohort SNP studies. Study-level risk-of-bias scoring is provided in Supplementary Table 2.

Results

Forty-four primary studies, published between 2003 and 2025, were included in the qualitative synthesis. The earliest was the description of CM-AVM syndrome linked to *RASA1* mutations (Eerola et al., 2003) [19]. For reasons of space, Table 1 summarises a representative selection of 26 key investigations, covering foundational germline discoveries and the major somatic drivers; the full list, with detailed methodological characteristics for all 44 included studies, appears in Supplementary Table 1.

Twenty-eight included primary studies were original clinico-genetic investigations, and 16 were experimental studies in animal models, cell-based systems, or both. A further 20 reviews and systematic reviews were used as contextual sources and for snowballing but were not counted as included studies [43, 65, 66, 82]. More than half of the primary studies appeared after 2018, mirroring wider uptake of high-sensitivity methods for detecting low-level somatic mosaicism [7, 22, 24, 26, 51, 59, 64]. For synthesis, the evidence was grouped into four thematic domains: (1) germline mutations and inherited AVM syndromes; (2) somatic mutations in sporadic AVMs; (3) molecular and epigenetic mechanisms; and (4) experimental models and *in vivo* validation [43, 66, 82].

Among inherited forms, *ENG* and *ACVRL1* variants (HHT1 and HHT2) were the commonest underlying causes [16, 37, 39, 44, 70, 80], with smaller contributions from *SMAD4* [14, 37] and loss-of-function *GDF2/BMP9* variants [18, 31]. Within the CM-AVM spectrum, *RASA1* was dominant [19, 62, 63], *EPHB4* underpinned CM-AVM2 [5, 92], and somatic mosaicism for *RASA1* accounted for cases without detectable germline variants [63]. In sporadic AVMs, somatic activating *KRAS* mutations emerged as the most consistent driver. The first signal came from Nikolaev et al. (45 of 72 cases) [51], confirmed and extended thereafter: Hong et al. reported 81.0% in brain (17/21) and 100% in spinal cord (10/10) lesions—87.1% combined across the CNS [33]; Priemer et al. 6 of 21 (28.6%) [59]; Goss et al. 10 of 16 (63%) [26]; and Gao et al. provided independent confirmation [24]. The pooled estimate from Bameri et al. is 55% for *KRAS* and 7.5% for *BRAF* [7].

Variant allele fractions sat consistently at low levels across studies, in keeping with somatic mosaicism and reinforcing the need for highly sensitive detection [7, 24, 26, 51, 59]. Endothelial-specific activation of *KRAS* or *BRAF* V600E reproduced AVM-like phenotypes *in vivo* and showed clear MEK–ERK dependence [22, 64, 79]. Several convergent epigenetic and post-transcriptional alterations have also been reported: aberrant DNA methylation [76, 77], *METTL3*-mediated m6A imbalance that perturbs Notch signalling [84], and exosomal miR-3131-driven endothelial-to-mesenchymal transition [30].

Genome-wide and candidate-gene studies have evaluated the 9p21 locus (rs1333040; *CDKN2B-AS1/ANRIL*) in sporadic AVMs. The GEN-AVM GWAS included 515 cases and 1,191 controls with an independent replication sample of 608 cases and 744 controls; no SNP replicated after multiple-testing correction, and the adjusted SNP-based heritability estimate was 17.6% (SE 8.9%) [85]. The rs1333040 result is described as a small, single-centre candidate-SNP association without external replication and is treated as hypothesis-generating [8, 9, 32, 46]. Genome-wide copy-number variation analyses have not identified replicated common CNVs associated with sporadic bAVM [8]. *IL6* and *TNFA* polymorphisms, by contrast, mapped more closely to haemorrhagic presentation [1, 25, 36, 55]; full details appear in Tables 1 and 2.

Table 1
Characteristics of key genetic studies on cerebral arteriovenous malformations included in the qualitative synthesis.

Authors, year (ref.)	Study design	Population / sample	Genes analyzed	Type of genetic alteration	Key findings	Methodology
Eerola et al., 2003 [19]	Family-based clinico-genetic study	17 families screened; 6 with <i>RASA1</i> mutations (human)	<i>RASA1</i>	Germline LOF	Description of CM-AVM syndrome; association of <i>RASA1</i> with AV shunts	Sanger sequencing; linkage analysis
Revenu et al., 2013 [62]	Cohort study	68 families (human)	<i>RASA1</i>	Germline mutations	Expanded CM-AVM phenotype; penetrance assessment	Sanger sequencing; MLPA
Revenu et al., 2020 [63]	Clinico-genetic study	4 index patients (human)	<i>RASA1</i>	Somatic mosaicism	Support for the "second-hit" model	Deep sequencing
Amyere et al., 2017 [5]	Cohort study	54 index patients with 47 distinct mutations (human)	<i>EPHB4</i>	Germline LOF	Description of CM-AVM2	Whole-exome sequencing (WES)
Snellings et al., 2019 [70]	Tissue-based genetic analysis	HHT vascular malformations (human)	<i>ENG, ACVRL1</i>	Somatic "second-hit" (biallelic loss)	Biallelic loss of <i>ENG</i> or <i>ACVRL1</i> in HHT vascular malformations	Ultra-deep NGS
Nikolaev et al., 2018 [51]	Clinical-genomic study	72 patients (WES in 26); <i>KRAS</i> in 45/72 (human)	<i>KRAS</i>	Somatic GOF	First evidence of <i>KRAS</i> as a driver in brain AVMs	WES + droplet digital PCR (ddPCR)
Priemer et al., 2019 [59]	Histopathology-based study	21 AVMs; <i>KRAS</i> -positive 6/21 (28.6%) (human)	<i>KRAS</i>	Somatic mutations	Clinicopathologic correlation with morphology	Targeted NGS
Hong et al., 2019 [33]	Cohort study	39 brain + 8 spinal cord AVMs (human)	<i>KRAS, BRAF</i>	Somatic mutations	<i>KRAS/BRAF</i> prevalence 81.0% in brain (17/21) and 100% in spinal cord (10/10) AVMs; combined CNS 87.1%	Targeted ddPCR
Goss et al., 2019 [26]	Cohort study	16 specimens; mutations in 10/16 (63%) (human)	<i>KRAS, BRAF</i>	Somatic mutations	Prevalence of MAPK pathway drivers	Targeted sequencing
Gao et al., 2021 [24]	Clinico-genetic study	14 WES + 56 validation = 70 samples (human)	<i>KRAS, BRAF</i>	Somatic mosaicism	Significant association between <i>KRAS</i> status/VAF and phenotype	Deep NGS
Fish et al., 2020 [22]	Experimental study	Mice	<i>KRAS</i>	Endothelial GOF	Endothelial <i>KRAS</i> activation is sufficient to induce AVM-like malformations	Transgenic mouse model
Saito et al., 2024 [64]	Experimental study	Mice	<i>KRAS</i>	CRISPR-based suppression	Reversal of the AVM phenotype in a <i>KRAS</i> -driven model	CRISPR/CasRx

Authors, year (ref.)	Study design	Population / sample	Genes analyzed	Type of genetic alteration	Key findings	Methodology
Tu et al., 2024 [79]	Experimental study	Mice	<i>BRAF</i>	GOF (V600E)	Endothelial <i>BRAF</i> V600E induces brain AVMs	Endothelial-specific knock-in
Kim et al., 2018 [37]	Experimental study	Mice	<i>SMAD4</i>	LOF	AVMs develop with <i>SMAD4</i> deficiency	Conditional knockout
Desroches-Castan et al., 2024 [18]	Experimental study	Mice	<i>GDF2</i> (BMP9)	LOF	BMP9 deficiency is sufficient to induce AVMs	Knockout mouse model
Zhu et al., 2019 [96]	Experimental study	Mice	<i>ALK1</i>	Somatic mutations	Induction of brain AVMs in the adult brain	CRISPR/Cas9
Walcott et al., 2018 [83]	Case-based genomics	1 patient (human)	BMP pathway	Somatic mutation	Genetic overlap between HHT-related and non-syndromic AVMs	WES
Thomas et al., 2022 [77]	Epigenomic study	2–3 AVM nidus samples (human)	—	DNA methylation	Epigenetic dysregulation within the AVM nidus	DNA methylation array
Wang et al., 2020 [84]	Functional study	AVM tissue + in vitro	<i>METTL3</i>	m6A dysregulation	<i>METTL3</i> -mediated Notch/TGF- β imbalance	RNA-seq; knockdown
He et al., 2023 [30]	Molecular study	AVMs (human)	<i>miR-3131</i>	Exosome-mediated regulation	Promotion of EndMT via PICK1	RNA-seq; exosome assays
Weinsheimer et al., 2016 [85]	Genome-wide association study	515 discovery + 608 replication (human)	<i>CDKN2B-AS1 (ANRIL)</i> / 9p21.3	SNP rs1333040	Common-SNP associations replicated; no genome-wide locus identified	GWAS
Bendjilali et al., 2014 [9]	Association study	338 cases (205 with aneurysm data; 74 with aneurysms) (human)	9p21.3 locus	SNPs	9p21.3 variants associated with brain AVMs accompanied by aneurysms	Genotyping
Pawlikowska et al., 2004 [55]	Candidate-gene association	180 AVMs (human)	<i>IL6</i> , <i>TNFA</i> + angiogenesis genes	SNPs	Inflammatory-pathway polymorphisms associated with hemorrhagic presentation	Candidate gene study
Achrol et al., 2007 [1]	Case–control association	216 AVMs (human)	<i>TNFA</i>	SNPs	TNF- α polymorphism associated with intracranial hemorrhage after AVM treatment	Case–control
Shimada et al., 2021 [68]	Experimental / tissue study	AVMs (human)	—	Neutrophil extracellular traps (NETs)	NETs in AVM inflammatory milieu	Immunohistochemistry
Soon et al., 2022 [72]	Experimental study	AVM-on-a-chip	<i>KRAS</i>	Somatic activation	Perfused human vessel-network model enabling drug testing	Microfluidic model

Table 2
Roles of genes and signaling pathways in the pathogenesis of cerebral arteriovenous malformations across stages of vascular development.

Stage of vascular development	Signaling axis / genes	Physiological role	Pathogenetic contribution in AVMs	Main evidence (key references)
Prenatal/perinatal (embryogenesis; early vascular organogenesis)	TGF- β /BMP9–ALK1– <i>ENG</i> –SMAD (<i>ENG</i> , <i>ACVRL1</i> /ALK1, <i>SMAD4</i> , <i>GDF2</i> /BMP9)	Limits sprouting; promotes vascular maturation; recruits pericytes/vascular smooth muscle cells; establishes arteriovenous specification.	Haploinsufficiency or LOF ("weak" maturation signal) predisposes to shunt formation under angiogenic triggers.	Human germline (HHT); mouse models of <i>Smad4/Alk1</i> deficiency and BMP9 loss [14, 16, 18, 37, 39, 44, 80].
Prenatal/perinatal	<i>RASA1</i> (CM-AVM1)	Negative regulation of endothelial RAS signaling; control of endothelial proliferation and vascular morphogenesis.	LOF $\rightarrow$ MAPK/ERK hyperactivation $\rightarrow$ arteriovenous shunts/micro-AVMs.	Human germline + mosaicism supporting "second-hit" mechanism [19, 62, 63, 92].
Prenatal/perinatal	<i>EPHB4</i> / EphB4–ephrinB2 (CM-AVM2)	Arteriovenous identity and artery–vein boundary; venous specification signaling.	LOF $\rightarrow$ impaired AV differentiation and shunting.	Human germline; pathway reviews [5, 92].
Pre-/postnatal	Notch (<i>NOTCH4</i> activation; endothelial Notch; pericyte RBPJ–Notch)	Arterial specification (DLL4–Notch), vascular network stabilization, endothelial–pericyte interactions.	Notch imbalance $\rightarrow$ AV identity defects and instability; pericyte Notch contributes to shunting.	Mouse models of constitutively active Notch4, endothelial Notch perturbation, pericyte Rbpj–Notch deficiency [11, 47, 48].
Postnatal (vascular maturation/remodeling)	Somatic MAPK drivers: <i>KRAS</i>	Regulates endothelial proliferation and migration (normally tightly regulated).	Hotspot GOF $\rightarrow$ clonal ERK activation $\rightarrow$ pathological angiogenesis and AV shunting.	Human somatic mutations in nidus; in vivo endothelial <i>KRAS</i> models [22, 24, 26, 51, 59, 64].
Postnatal	Somatic MAPK drivers: <i>BRAF</i> V600E	Regulation of MAPK/ERK cascade.	GOF $\rightarrow$ endothelial dysfunction and AVM-like phenotype; potential therapeutic target.	Experimental models and <i>BRAF</i> V600E endothelial models [24, 26, 33, 79].
Postnatal	ALK1/ <i>ENG</i> "second hit" / somatic events in TGF- β /BMP axis	Maintenance of postnatal vascular maturation and network stabilization.	Somatic inactivation of <i>Alk1</i> $\rightarrow$ focal AVM-like lesions; supports two-hit model.	Biallelic loss in HHT lesions; CRISPR-induced somatic <i>Alk1</i> mutations [70, 96].
Postnatal (wall structure, stability)	Pericytes and endothelial–pericyte interactions	Barrier function, mechanical support, capillary stabilization.	Reduced pericyte coverage $\rightarrow$ wall fragility.	AVM morphology + CNS pericyte biology; pericyte Notch [48, 86, 87].
Postnatal (inflammation / matrix remodeling)	Inflammation + proteases (NETs; MMP/TIMP)	Controlled extracellular matrix remodeling.	Chronic inflammation/NETs $\rightarrow$ matrix degradation, increased wall vulnerability, hemorrhage risk.	Human evidence for NETs and MMP/TIMP dysregulation [29, 68].
Postnatal (epigenetic regulation)	m6A–Notch regulation (<i>METTL3</i>); DNA methylation; miRNA / exosomes	Post-transcriptional and epigenetic tuning of differentiation programs.	Aberrant methylation/m6A $\rightarrow$ altered Notch/TGF- β balance; exosomal miRNAs propagate pathological program (EndMT).	Human tissue and cell-based functional studies [23, 30, 76, 77, 84].
Phenotype modifiers	GWAS: 9p21/ <i>ANRIL</i> (<i>CDKN2B-AS1</i> ; rs1333040);	Regulation of proliferation; inflammatory response.	Small effects on AVM susceptibility and on hemorrhagic presentation/recurrence.	GWAS + replication [1, 9, 25, 46, 55, 85].

Stage of vascular development	Signaling axis / genes	Physiological role	Pathogenetic contribution in AVMs	Main evidence (key references)
	inflammatory SNPs (<i>IL6</i> , <i>TNFA</i>)			
Postnatal (translational platforms)	In vitro/perfused AVM-on-a-chip	Recapitulation of network architecture and stimulus responses.	Modeling key disease hallmarks; drug testing.	Human-derived AVM-on-a-chip [72].

Genetic landscape of cerebral AVMs

Germline mutations in syndromic AVMs: hereditary hemorrhagic telangiectasia

Much of the hereditary susceptibility to bAVMs comes from autosomal-dominant vascular syndromes, HHT above all [44]. Classically, HHT is linked to germline variants in *ENG* and *ACVRL1* (encoding *ALK1*), and less commonly in *SMAD4* and *GDF2*—genes that all converge on the TGF-β/BMP signalling axis [14–16, 18, 31, 37, 39, 44, 80].

ENG encodes endoglin, an endothelial TGF-β co-receptor; loss-of-function variants disrupt TGF-β/BMP signal transduction and compromise vessel-wall maturation [39, 44]. *ACVRL1* encodes the receptor kinase *ALK1*, a central endothelial mediator of the BMP9/BMP10 ligand network [15, 16, 31, 80]. *SMAD4* variants give rise to inherited vascular anomalies and an AVM phenotype within *SMAD*-mediated TGF-β/BMP disruption [14, 37]. Loss-of-function in *GDF2/BMP9* produces an AVM-like phenotype in experimental models [18, 31]. The marked phenotypic variability seen in patients carrying the same germline variant fits with local modifying events and/or somatic mosaicism, as molecular work in HHT patients has now confirmed [70].

Germline mutations in clinically isolated AVMs: CM-AVM spectrum

CM-AVM syndromes can present as apparently isolated arteriovenous malformations—including cerebral lesions—accompanied by cutaneous capillary malformations and AV shunts [19, 62, 92]. The commonest cause is a germline variant in *RASA1*, which encodes a RasGAP regulator [19, 62, 92]; *EPHB4* variants underlie CM-AVM2 and overlap phenotypically with *RASA1* disease [5, 88, 92]. In some patients, low-VAF mosaic *RASA1* variants explain the absence of a detectable germline mutation [63], which fits a "predisposition plus local somatic event" model for CM-AVM [63, 92].

Rare germline causes of cerebral AVMs

Beyond HHT and CM-AVM, several rare inherited causes have been described. Biallelic *DYNC1I2* variants produce a syndromic microcephaly phenotype—vascular malformations are not an established feature, but the case illustrates the wider genetic heterogeneity of rare cerebral developmental disorders [6]. *PTEN*-related conditions (the Cowden/*PTEN* hamartoma tumour spectrum) can include vascular manifestations and broaden the relevant pathway repertoire [57, 75]. Familial case reports and locus-mapping studies have also been described for familial cerebral AVMs [52, 91].

Somatic mutations in sporadic cerebral AVMs

Most cerebral AVMs are sporadic. The identification of somatic activating variants in the RAS/MAPK cascade reshaped the field [7, 24, 26, 33, 51, 59, 66, 82]. Nikolaev et al. (2018) provided the first solid evidence of somatic gain-of-function *KRAS* mutations in sporadic cerebral AVM tissue, with most variants at canonical hotspots linked to constitutive MAPK/ERK activation [51]. Subsequent cohort studies confirmed these findings and added detail on the frequency and clinico-pathological correlates of *KRAS* variants [24, 26, 33, 59]. Systematic reviews support a dominant role for *KRAS/BRAF* alterations in sporadic cerebral AVMs [7]. Across these studies the variant allele fraction stays low, consistent with somatic mosaicism and reinforcing the need for highly sensitive detection [7, 24, 26, 51, 59].

MAPK pathway activation has now been validated experimentally. Endothelial-specific *KRAS* activation is sufficient to drive vascular malformations and AV shunting in a MEK-dependent manner [22]. RNA-targeting approaches against *KRAS* transcripts further suggest disease modulation is feasible and reinforce a causal role for the *KRAS*–ERK axis [64]. Other models indicate *KRAS* activation produces capillary network defects with reduced pericyte coverage, linking the initiating event to vessel-wall instability [74]. Endothelial *BRAF*

V600E reproduces an AVM-like phenotype in vivo [79]. Taken together, local clonal MAPK activation in endothelial cells sits at the heart of sporadic cerebral AVM biology, tipping the balance between proliferation, angiogenesis, and vascular maturation [7, 22, 24, 26, 51, 59, 64, 66, 74, 79, 82].

Genetic susceptibility polymorphisms in sporadic cerebral AVMs

Unlike syndromic germline mutations and somatic drivers, single-nucleotide polymorphisms (SNPs) are not sufficient to cause cerebral AVMs on their own, but they appear to modify individual risk and clinical behaviour, including haemorrhagic complications [1, 8, 9, 25, 36, 46, 55, 85]. The most consistent susceptibility signal is rs1333040 at 9p21 (CDKN2B-AS1/ANRIL), identified by GWAS [85]; supporting copy-number-variation evidence has been reported [8], with broader synthesis in meta-analytic and review work [25, 46]. Functionally, the long non-coding RNA ANRIL has been put forward as a key intermediary linking 9p21 variation to vascular remodelling, inflammation, and vessel-wall pathology [32].

Inflammatory polymorphisms appear more closely tied to haemorrhagic presentation and vessel-wall instability. IL6 and TNF α variants have been associated with haemorrhagic presentation in candidate-gene studies [55], and the TNF- α – 238G > A variant with intracranial haemorrhage after AVM treatment [1]. 9p21.3 variants have also been linked to AVMs with arterial aneurysms [9]. On balance, SNP data suggest genetic modifiers do not by themselves determine whether an AVM forms, but they may shape vessel-wall vulnerability and haemorrhagic manifestations through interactions with somatic driver events and local inflammatory mechanisms [1, 8, 9, 25, 36, 46, 55, 66, 82, 85].

Discussion

This review reinforces the view of cerebral AVMs as a genetically and biologically heterogeneous entity, in which germline variants, somatic mutations, and risk modifiers converge on a small set of signalling axes that govern angiogenesis, arteriovenous specification, and vessel-wall maturation [43, 66, 82]. The central problem appears to be an imbalance between pro-angiogenic stimuli and the differentiation and stabilisation programmes that hold them in check—driven by syndromic TGF- β /BMP defects and somatic KRAS/MAPK events, and further shaped by inflammation, hypoxia, and haemodynamics [22, 35, 41, 50, 64, 66, 82].

Recent reviews have set out the role of the KRAS/MAPK pathway in sporadic brain AVMs and across vascular anomalies in considerable detail [65, 66, 82, 90]. Our synthesis adds to that picture by holding the focus tightly on cerebral parenchymal lesions and by placing low-VAF somatic tissue evidence next to in vivo causality models. The molecular drivers are increasingly well defined, even as the use of genetic profiling in routine neurosurgical workflows remains held back by limits in analytical sensitivity and tissue availability.

For syndromic forms (HHT, CM-AVM), the most consistent evidence points to a primary germline defect at one of the key TGF- β /BMP nodes (ENG, ACVRL1/ALK1, SMAD4, GDF2/BMP9) or in RAS regulation and AV specification (RASA1, EPHB4). This sets a vulnerable vascular background, but penetrance is incomplete and phenotypic variability is striking [5, 14, 16, 18, 19, 31, 37, 39, 44, 62, 63, 92]. Somatic mosaicism and "second-hit" mechanisms in HHT speak to a need for local modifying events in at least a subset of patients [70]. For sporadic MAPK-driven lesions, a single endothelial somatic event may suffice to start an AVM-like phenotype [22, 28, 37, 64, 79, 96].

The timing of AVM development represents a critical distinction between human pathology and experimental models. Current evidence, as summarized in Table 2, suggests that germline mutations establish a developmental vascular susceptibility during the prenatal or perinatal stages. Conversely, as detailed in our analysis of primary studies (Supplementary Table 1), experimental models have robustly demonstrated that somatic MAPK-driven AVM-like lesions (e.g., KRAS or BRAF mutations) can be induced postnatally.

A turning point in the field was the discovery of somatic activating KRAS, and less commonly BRAF, mutations in sporadic cerebral AVM tissue—evidence consistent with a local clonal endothelial event [7, 24, 26, 51, 59]. Endothelial-specific KRAS activation drives vascular malformations in a MEK/ERK-dependent fashion, placing the MAPK pathway on solid biological ground as a preclinical target; concordant findings come from genetic suppression of KRAS and from BRAF V600E endothelial models [22, 64, 79]. MAPK dysregulation tips the balance between endothelial growth and vascular maturation, favouring AV shunting and an unstable vessel-wall phenotype [22, 40, 66, 82]. Somatic KRAS/BRAF variants are most plausibly tied to lesion initiation and growth, whereas the risk of rupture is shaped more by vessel-wall integrity, inflammation, extracellular-matrix remodelling, and haemodynamics [7, 35, 41, 59, 66, 82].

Local endothelial signalling noise—epigenetic, post-transcriptional, and paracrine—further shapes the phenotype. Inflammation, matrix degradation, and neutrophil extracellular traps within cerebral AVM tissue point to a self-sustaining local inflammatory loop that keeps remodelling going and weakens the vessel wall [29, 66, 68, 82]. Persistently low VAFs fit with mosaicism and paracrine effects from surrounding non-mutant cells; a negative test may therefore reflect limited analytical sensitivity, sampling limitations, or contributions from variants outside standard panels and from epigenetic mechanisms [7, 24, 26, 51, 59, 66, 67, 82]. Data on DNA methylation, m6A modification, and microRNA/exosome biology implicate Notch/TGF- β balance and angiogenic regulation, although standardisation and replication remain needed [23, 30, 76, 77, 84].

SNP associations—the 9p21/ANRIL signals and inflammatory or angiogenic variants—typically have small effect sizes for whether an AVM exists at all, yet may act as modifiers of an aggressive or haemorrhagic course [1, 8, 9, 25, 36, 46, 55, 85]. This fits a framework in which somatic driver events answer why a lesion arises, while modifiers and tissue-level mechanisms help explain why a given course turns aggressive [1, 25, 36, 55, 66, 82]. KRAS- and BRAF-driven models, together with somatic perturbations of the ALK1/SMAD4/BMP9 axis, have opened the door to preclinical testing of pharmacological and genetic interventions [18, 22, 28, 37, 49, 64, 79, 96]. Preclinical work tentatively suggests that intervening during phases of active remodelling may be more tractable than reversing an established AVM architecture [64, 79], though human evidence is still lacking. Systematic risk of bias should be kept in mind for preclinical findings, with tools such as SYRCLE applied [34].

Cerebral AVM endothelium can express lymphatic-associated genes, taken as support for a "loss of vascular identity" or shifts in differentiation programmes [69]. Regulators of physiological angiogenic sprouting—notably the neuropilin-1–CDC42 axis—provide the background against which MAPK, Notch, and TGF- β /BMP dysregulation play out [21]. Vessel-wall stability depends on pericytes and Notch signalling, and dysregulated endothelial Notch can yield reversible AV phenotypes once the pathological signal is switched off [11, 48, 86, 87]. The parallels are striking: extracranial AVMs with somatic MAP2K1; PIK3CA-driven venous and lymphatic malformations, including PROS; sporadic cavernous malformations carrying somatic PIK3CA; and vein-of-Galen malformations—together suggesting that postzygotic variants in key cascades shape disease phenotype and may determine sensitivity to targeted therapy [13, 56, 93, 94].

Hypoxia and haemodynamics further shape the disease. In resected cerebral AVM specimens, HIF-1 α expression tracks with that of VEGF and its receptors, supporting a HIF-1 α →VEGF/VEGFR axis [50]. ANGPTL4 is induced by hypoxia and modulates both angiogenesis and vascular permeability; ANGPTL4 polymorphisms have been linked to bAVM risk in some cohorts, with mixed findings in others [20, 38, 45]. Persistent haemodynamic changes, together with quantitative features derived from arteriography, have shown predictive value for later haemorrhage in untreated lesions [35, 41], and AV shunting can develop secondarily within pre-existing venous anomalies [58].

Translational evidence for anti-angiogenic strategies is most mature for syndromic disease, particularly HHT. Bevacizumab has been effective in severe visceral vascular malformations, and safety data exist for both bevacizumab and thalidomide [10, 81]. In preclinical murine models of cerebral AVMs, AAV-delivered soluble FLT1 and dual MAPK/VEGF inhibition have been explored, though translation to human cerebral AVMs is not yet established [49, 95]; perfused AVM-on-a-chip platforms are emerging as a new tool for drug testing [72].

Implications for neurosurgical practice. First, genetic counselling and screening for HHT or CM-AVM are worth considering in patients with multiple lesions, a positive family history, or characteristic mucocutaneous features. Second, MAPK-targeted therapies remain investigational for cerebral AVMs and are not yet an alternative to microsurgery, radiosurgery, or embolisation. Routine somatic KRAS/BRAF testing on resected nidus tissue is not standard of care, largely because detecting low-VAF mosaicism is technically demanding; a negative test does not, on its own, rule out a somatic origin. Finally, somatic drivers cannot reliably predict clinical behaviour or haemorrhagic risk in an unruptured AVM, which still depend on angiographic features, patient age, and structural haemodynamics.

Limitations and future directions.

A critical appraisal of the evidence base raises several caveats:

Language restriction: searches were limited to English- and Russian-language publications, which may have left out relevant evidence reported in other languages.

Clinical and methodological heterogeneity: differences in study design, cohort definition, tissue handling, and sequencing strategy were too large to support a quantitative meta-analysis; the findings are therefore presented as a structured qualitative synthesis.

Publication bias: with the heterogeneity in designs and outcomes, formal tests such as funnel plots or Egger's test were not feasible, and selective reporting of positive molecular findings cannot be ruled out.

Tissue-sampling bias: the case for KRAS/BRAF somatic drivers is strong but rests largely on surgically accessible, resected tissue, which may not capture the biology of unruptured or deep-seated lesions.

Analytical sensitivity: estimates of somatic mutation frequency depend heavily on assay design, sequencing depth, and the endothelial-enrichment protocol used.

Haemorrhage-risk genetics: the genetic determinants of clinical behaviour and rupture remain statistically underpowered and lean heavily on heterogeneous SNP data.

Translational gaps: animal models capture causality well—KRAS-induced shunting is a clear example—but they do not reproduce the chronological evolution of human cerebrovascular lesions in full.

A methodological caveat for the review itself is the lack of prospective protocol registration (e.g., in PROSPERO). We tried to offset this by adhering strictly to predefined inclusion criteria and to PRISMA guidelines throughout.

Promising directions include: (i) standardising highly sensitive protocols for low-VAF and tissue-specific mosaicism detection; (ii) single-cell approaches—including the recent human brain vascular atlas—to chart cellular states and intercellular interactions; and (iii) bringing genetic data together with haemodynamic and clinical predictors of rupture risk [35, 41, 42, 60, 89, 90].

Conclusion

Cerebral arteriovenous malformations are genetically and molecularly heterogeneous lesions driven by a convergence of germline predispositions and somatic endothelial events. However, it is crucial to strictly distinguish between established human evidence and experimental inferences. While human tissue studies have robustly identified somatic KRAS/MAPK drivers and germline variants in syndromic forms, data linking specific genotypes to clinical phenotypes or rupture risk remain limited and heavily confounded by selection bias. Furthermore, the rationale for targeted therapies is currently derived predominantly from preclinical animal models and cannot yet be extrapolated to human clinical practice. The molecular landscape of unruptured or deep-seated AVMs remains largely unexplored, and the detection of somatic mosaicism is highly assay-dependent. Future progress in molecularly informed neurosurgery requires overcoming significant translational gaps, including the standardization of high-sensitivity assays, prospective validation of genotype-phenotype correlations in unselected human cohorts, and rigorous safety profiling of pathway-targeted interventions.

Abbreviations

ACVRL1 — activin A receptor-like type 1 (gene; encodes ALK1)

ALK1 — activin receptor-like kinase 1

ANGPTL4 — angiopoietin-like 4

ANRIL — antisense non-coding RNA in the INK4 locus (CDKN2B-AS1)

AV — arteriovenous

AVM — arteriovenous malformation

bAVM — brain arteriovenous malformation

BMP — bone morphogenetic protein

BRAF — B-Raf proto-oncogene

CM-AVM — capillary malformation–arteriovenous malformation

CRISPR — clustered regularly interspaced short palindromic repeats

ddPCR — droplet digital polymerase chain reaction

EndMT — endothelial-to-mesenchymal transition

ENG — endoglin

EPHB4 — ephrin receptor B4 (gene)

ERK — extracellular signal-regulated kinase

GDF2 — growth differentiation factor 2 (encodes BMP9)

GOF — gain of function

GWAS — genome-wide association study

HHT — hereditary hemorrhagic telangiectasia

HIF-1 α — hypoxia-inducible factor 1 alpha

KRAS — Kirsten rat sarcoma viral oncogene homolog

LOF — loss of function

m6A — N6-methyladenosine

MAP2K1 — mitogen-activated protein kinase kinase 1 (MEK1)

MAPK — mitogen-activated protein kinase

MEK — MAPK/ERK kinase

METTL3 — methyltransferase-like 3

NETs — neutrophil extracellular traps

NGS — next-generation sequencing

PIK3CA — phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

PRISMA — Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTEN — phosphatase and tensin homolog

RAS — RAS family of small GTPases

RASA1 — RAS p21 protein activator 1

SMAD4 — SMAD family member 4

SNP — single-nucleotide polymorphism

TGF- β — transforming growth factor beta

TNF- α — tumor necrosis factor alpha

VAF — variant allele fraction

VEGF — vascular endothelial growth factor

Statements and Declarations

Funding. This research was funded by the Ministry of Science and Higher Education of the Russian Federation, grant number 075-15-2024-561.

Competing interests. The authors have no relevant financial or non-financial interests to disclose.

Ethics approval. Not applicable. This article does not contain any new studies with human participants or animals performed by any of the authors.

Consent to participate. Not applicable.

Consent to publish. Not applicable.

Data availability. All data analyzed in this study are derived from published literature and are summarized in the main text and tables.

Code availability. Not applicable.

Registration. This systematic review was not prospectively registered in PROSPERO.

Clinical trial number: Not applicable.

Use of Artificial Intelligence. The authors used a generative AI tool (OpenAI ChatGPT) for graphical-layout assistance with Figure 2 only. All generated visual content was reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the final figure.

Author contributions. Conceptualization: A.N.K., G.P., S.S.E. Methodology: A.N.K., F.G., D.O. Literature search and study selection: F.G., D.O., O.B. Data extraction and curation: F.G., D.O., O.B. Formal analysis and synthesis: A.N.K., F.G., Y.P., D.O. Writing—original draft: A.N.K., F.G. Writing—review and editing: all authors. Supervision: A.N.K., S.S.E. All authors read and approved the final manuscript.

Acknowledgments. The authors thank the colleagues at the N.N. Burdenko National Medical Research Center of Neurosurgery for helpful discussions during preparation of this review.

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Figures

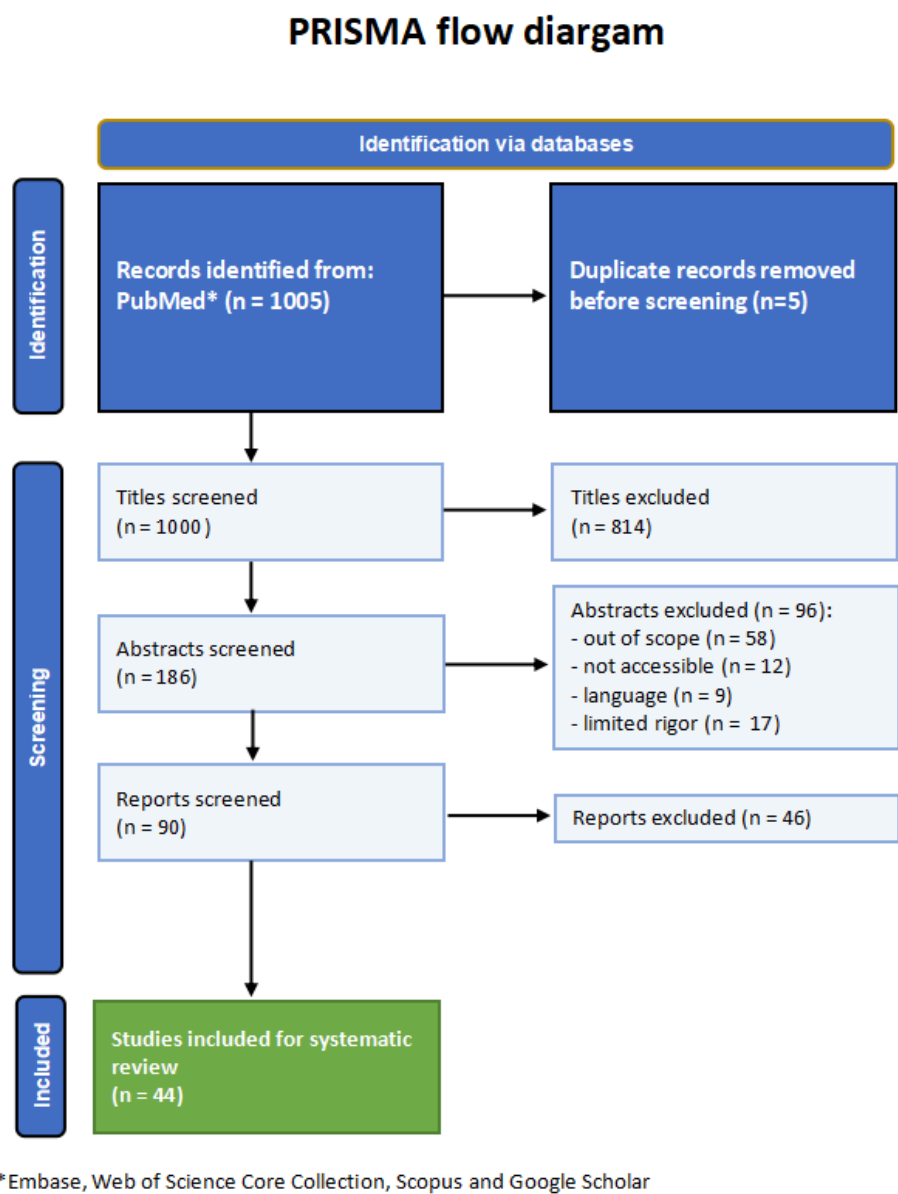


Figure 1

PRISMA 2020 flow diagram illustrating the literature selection process for the systematic review on the impact of genetic factors on the formation of cerebral arteriovenous malformations.

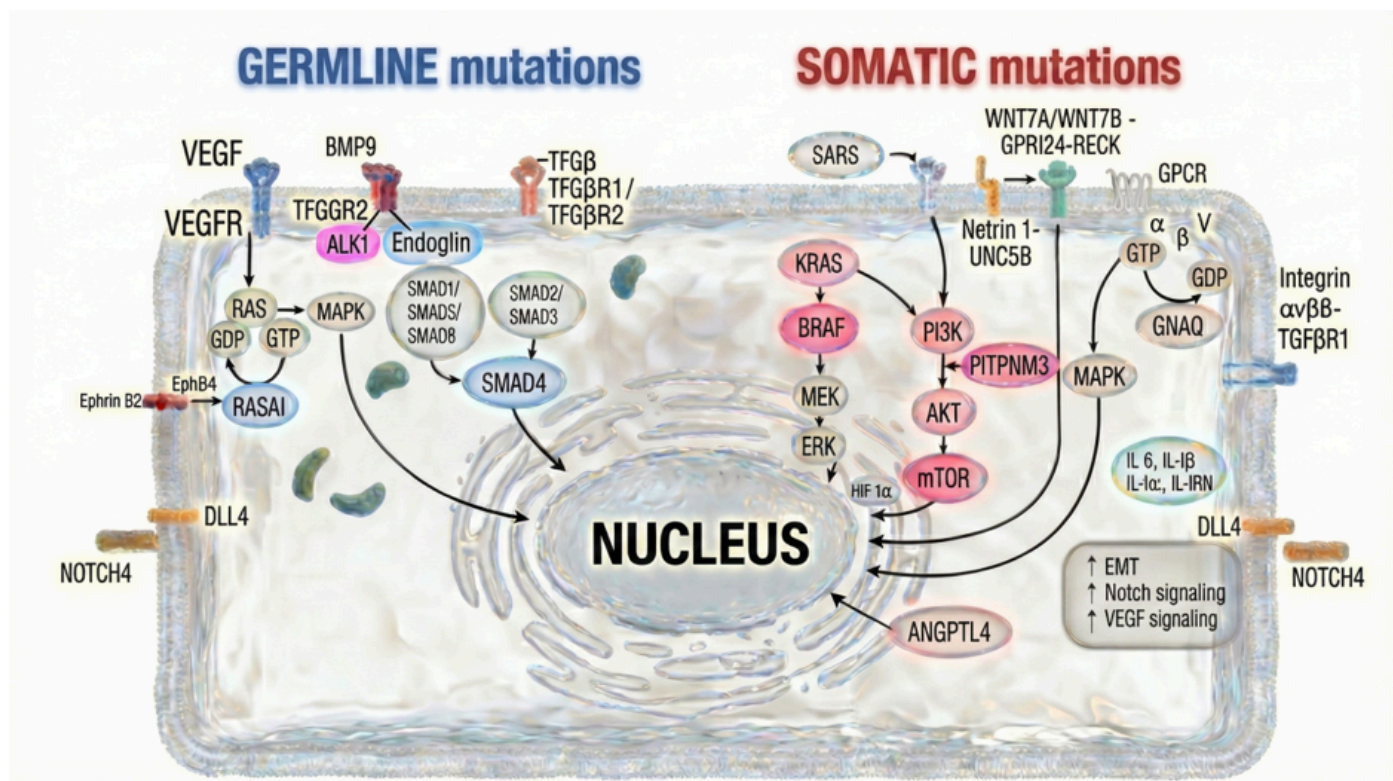


Figure 2

Integrative molecular model of cerebral arteriovenous malformation pathogenesis. Cerebral AVMs arise from the converging effects of germline predisposition and somatic driver mutations in endothelial signalling. Germline defects in TGF- β /BMP (ENG, ACVRL1, SMAD4) or in the arteriovenous-specification pathway (RASA1, EPHB4) set a vulnerable vascular background, while somatic activating mutations in MAPK cascade components (KRAS, BRAF, MAP2K1) act as local clonal drivers in sporadic lesions. These changes unbalance endothelial proliferation against vessel maturation, impairing pericyte recruitment and amplifying angiogenic signalling. Inflammatory stimuli, extracellular-matrix remodelling, susceptibility polymorphisms, and haemodynamic stress all add to the vascular instability, eventually producing direct arteriovenous shunting and an elevated haemorrhagic risk.

Supplementary Files

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- [SupplementaryTable1.docx](#)