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Detection rate and mutational landscape in extracranial arteriovenous malformations: a cohort study

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Abstract

Background This study aimed to assess the detection rate and spectrum of pathogenic variants (PVs) and candidate variants (variants of uncertain significance, VUS) in AVM patients.

Methods In this retrospective multicenter cohort study, tissue and blood samples were collected from 114 patients with extracranial AVMs during treatment or when clinically indicated, for dedicated molecular genetic analyses. PVs (solved) and VUS were detected by targeted sequencing on DNA using gene panels analyzing genes suspected to be associated with AVMs. Unsolved cases were further categorized into unrestricted and restricted, with the latter reflecting methodological limitations. Subgroup analyses were carried out based on affected genes to explore associated genotype–phenotype correlations.

Results PVs were identified in 80.7% (92/114) and VUS in 5.3% (6/114), resulting in a total detection rate of 86.0% (98/114). Unsolved cases accounted for 11.4% (13/114) including 6/13 (46.2%) with methodological restrictions. Somatic PVs were most frequent in *KRAS* (21.1%, 24/114), *MAP2K1* (17.5%, 20/114), *HRAS* (8.8%, 10/114), and *BRAF* (7.9%, 9/114). Germline variants were found in *RASA1* (7.0%, 8/114), *PTEN* (5.3%, 6/114), and *EPHB4* (3.5%, 4/114). In a few cases, somatic variants in *RASA1* (1.8%, 2/114) and *PTEN* (2.6%, 3/114) were identified. Additional PVs occurred in *PIK3CA* (3.5%, 4/114), *SOS1* (2.6%, 3/114), *GNAQ* (1.8%, 2/114), and *RIT1*, *RAF1*, and *GNA14* (each 0.9%, 1/114). Within the RAS/MAPK pathway, *RAS* variants (*KRAS*, *HRAS*) were linked to more severe clinical stages (65.6% vs. 40.0% *MAP2K1* and 37.5% *BRAF*, $p=0.027$) and higher relapse rates (55.6% vs. 43.8% *MAP2K1* and 0% *BRAF*, $p=0.049$). Germline variants showed a distinct distribution pattern with more syndromic presentations (61.1% vs. 15.6%, $p<0.001$) compared to mosaic variants.

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Conclusions Broad and sensitive testing enables a high detection rate of causative variants in AVMs. PVs and VUS detected reveal a broader genetic spectrum than previously recognized. Somatic *RAS* PVs were associated with more advanced disease stages and higher relapse rates than *MAP2K1* and *BRAF* variants, while germline variants were more frequently linked to syndromic patterns.

Keywords Arteriovenous malformations, AVM, Mosaicism, Pathogenic variants, Detection rate

Background

Vascular malformations are congenital anomalies that are further classified into developmental anomalies of named vessels, slow-flow malformations (predominantly venous and lymphatic) as well as fast-flow arteriovenous malformations (AVMs). AVMs are associated with higher morbidity, risk of rapid progression, and challenging treatment [1–3]. Complete remission is often not achievable, and residual lesions typically continue to progress. The 2025 update of the ISSVA classification emphasized the integration of genetic findings, deepening insight into the pathogenesis of these rare lesions. Expanding knowledge into the genetic and molecular basis of vascular malformations have reshaped the understanding of their disease mechanisms, paving the way for improved patient stratification and individualized therapeutic approaches [4, 5]. Sporadic vascular malformations are frequently caused by somatic gain-of-function variants in genes encoding components of key signaling pathways that regulate cell growth and differentiation [6]. The broad spectrum of clinical phenotypes is thought to reflect the affected cell type, the timing of the mutational event, and the extent and nature of pathway activation. In conditions caused by mutations affecting the PI3K/AKT/mTOR signaling pathway, genotype-based stratification has led to early clinical trials of targeted therapies [7]. While vascular malformations were historically regarded as static dysplastic anomalies, increasing evidence of activated growth- and proliferation-related pathways suggests that these lesions possess proliferative potential [8]. Within this context, robust cohorts providing reliable data on detection rates, defining the variant spectrum, and clarifying genotype–phenotype associations are still lacking. Here, we present a multicenter study in which ultra-deep next-generation sequencing of DNA samples from affected tissue or blood identified pathogenic variants (PVs), report their detection rate, and analyze genotype–phenotype correlations with potential clinical implications.

Methods

Aim of the study

This study primarily aimed to report the diagnostic yield and mutational landscape following molecular genetic

testing in a multicenter AVMs cohort, and secondarily to analyze genotype–phenotype correlations with potential clinical implications. Clinical features, lesion extension, and progression rates are included as part of the phenotype.

Patient cohort and sample collection

This retrospective multicenter cohort study was conducted among interdisciplinary vascular anomalies centers of six university hospitals in Germany. Included are patients with a clinical diagnosis of AVM, who were selected for genetic testing between 2019 and 2025. All genetic analyses were performed based on clinical indications. In accordance with national regulations (German Genetic Diagnostics Act, GenDG), all participants provided informed consent for diagnostic testing as well as for the scientific use of the results, including radiological and clinical images. Furthermore, retrospective analyses were approved by the local ethics committee (University Hospital, LMU Munich, protocol no: 23–0337). The Strengthening the Reporting of Genetic Association Studies (STREGA) [9] guidelines were used for appropriate reporting, see Additional file 1: Table 1. In general, off-label therapy (e.g., trametinib or dabrafenib) was available for patients at all participating centers and could be reimbursed by the patients' insurance providers after approval of individual cost-coverage applications, as no suitable clinical trials were recruiting.

Part of the cohort (22/114 patients) has already been published previously, see Additional file 2: Table 2 [5]. Core needle biopsies were performed under ultrasound guidance close to the AVM nidus. All patients with AVMs that underwent molecular genetic testing within the specified period were included, regardless of whether a PV was detected or not. Analysis was performed in corresponding fresh or formalin-fixed, paraffin-embedded (FFPE) tissue, or ethylenediaminetetraacetic acid (EDTA) blood. Exclusion criteria were clinical, pathological, or radiological doubts regarding the diagnosis of an AVM. Thus, detection rate of PVs (solved) and of candidate variants (variants of uncertain significance, VUS), as well as the rate of unsolved cases were calculated. Unsolved cases were further categorized into unrestricted and restricted genetic testing. In the latter, methodological limitations may explain the absence of detectable variants

in the corresponding sample (e.g. availability of leukocyte DNA only, poor DNA quality of FFPE samples). Demographics, medical history, clinical, and radiological data as well as treatment course and follow-up assessments were collected. Clinical suspicion of disease recurrence was confirmed by MRI. Disease progression was defined as increase or reoccurrence of clinical symptoms after treatment as well as increased lesion size or newly perfused vessels compared to preceding imaging findings.

Details about DNA extraction, variant screening, and genetic analysis are listed in the Additional file 3. The gene content also evolved over time (a complete list of genes/gene hotspots covered by the employed enrichment kit is available in Additional file 4: Table 3).

Statistics

Data are presented as mean ($\pm$ SD) or median (range, minimum–maximum). Subgroup analyses were performed related to the affected genes or to defined variant groups according to overarching features (e.g. germline versus mosaic variants). Cramers' V test and Fisher's exact test (if $n < 5$ in $> 20\%$ of cell counts) were applied for categorical data and small sample sizes to assess the association of the different PV carriers or group with clinical phenotypes such as lesion localization, lesion tissue involvement (one versus several tissue types), Cho and Schobinger classification, relapse (yes/no), and distribution pattern (isolated, multifocal, syndromic) according to 2025 ISSVA classification [10]. Multifocal lesions were defined as the presence of two or more anatomically distinct vascular malformations in the same patient (e.g., CM-AVM), without association with additional congenital anomalies or systemic features. Syndromic lesion was defined as an AVM occurring as part of a clinically recognizable syndrome, in association with other congenital anomalies or systemic manifestations (e.g., soft tissue or skeletal hypertrophy). Binary and multinomial logistic regression models were performed to examine potential confounders, including age, sex, and treatment methods. Analysis was conducted using SPSS (Version 26.0, Armonk, NY: IBM Corp.), all p-values reported are two-tailed.

Results

Patient characteristics and clinical presentation

All patients included ($n = 114$, 100%) presented with clinically and radiologically confirmed extracranial AVMs [10], and were managed interdisciplinarily according to clinical features, Schobinger stage [11], and patient preference (embolization, surgery/amputation, laser, targeted medical therapy, observation). The cohort consisted of 60/114 (52.6%) females and 54/114 (47.4%) males as well as 49/114 (43.0%) children (< 18 years, mean age of

8.9 years $\pm$ 4.7 years). Genetic testing was performed at a mean age of 22.3 years ($\pm$ 14.7 years). AVMs were located on lower extremities in 43/114 patients (37.7%), followed by head and neck (33/114, 28.9%), upper extremities (14/114, 12.3%), trunk (7/114, 6.1%), and parenchymatous organs (2/114, 1.8%). The remaining lesions (15/114, 17.2%) extensively involved two or more anatomical regions (Table 1). Related to affected tissue types (cutaneous, subcutaneous, intramuscular, intraosseous, parenchymatous, nerve), 35/114 AVMs (30.7%) were limited to one type, 79/114 (69.3%) AVMs involved several types (Table 1). An extension of the AVM into parts of the central nervous system was observed in 6/114 patients (5.3%). The clinical stage of AVMs according to Schobinger [11] ($n = 110$) presented as follows: stage 1 (12/110, 10.9%), stage 2 (44/110, 40.0%), stage 3 (47/110, 42.7%), and stage 4 (7/110, 6.4%). AVMs were classified angiographically according to Cho [12] ($n = 96$): type I (2/96, 2.1%), type II (8/96, 8.3%), type IIIa (37/96, 38.5%), and type IIIb (49/96, 51.0%; Table 1).

Treatment course and follow-up

In 49/114 (43.0%) cases, the AVMs were treated by minimally invasive interventional radiology (embolotherapy), in 23/114 (20.2%) patients a combined approach of IR and surgical resection and in 11/114 (9.6%) of IR and targeted medical therapy. Six of 114 (5.3%) patients underwent surgery alone, 3/114 (2.6%) targeted medical therapies alone, and 12/114 (10.5%) patients did not undergo any treatment. The median number of invasive treatment sessions was 3 (0–41), the median follow-up time 22 months (7–36 months). Overall, 32 of 76 patients with follow-up data (42.1%) experienced a relapse in the clinical course after treatment. At the last follow-up, 14/83 (16.9%) lesions demonstrated complete regression, 50/83 (60.2%) partial regression, 14/83 (16.9%) AVMs remained stable, while 5/83 (6.0%) showed progression. In 43/114 patients (37.7%; based on the detected variants: 43/98, 43.9%), clinical management was modified according to the genetic findings, with subsequent initiation of targeted medical therapy in 12/114 cases (10.5%; 12/98, 12.2%), impact on family counseling in 18/114 cases (15.8%; 18/98, 18.4%), or even revision of the clinically suspected diagnosis in 13/114 cases (11.4%; 13/98, 13.3%). Treatment modalities and types of targeted medical therapy are detailed in Table 2.

Detection rate and spectrum of PVs

PVs (pathogenic or likely pathogenic variants) were found in 80.7% (92/114) and candidate variants (variants of uncertain significance, VUS) in 5.3% (6/114), resulting in a total detection rate of 86.0% (98/114, Fig. 1). Thirteen of 114 cases (11.4%) remained

Table 1 Patient characteristics and clinical presentation of study cohort

	Total cohort
Age (years)	
Mean ($\pm$ SD)	22.3 ($\pm$ 14.7)
Sex	
Female	60/114 (52.6%)
Lesion localization	
Lower Extremity	43/114 (37.7%)
Head and neck	33/114 (28.9%)
Upper extremity	14/114 (12.3%)
Trunk	7/114 (6.1%)
Intraabdominal	2/114 (1.8%)
Extensive lesions (> 1 anatomical regions)	15/114 (13.2%)
Cho classification for AVMs*	
I	2/96 (2.1%)
II	8/96 (8.3%)
IIIa	37/96 (38.5%)
IIIb	49/96 (51.0%)
Schobinger classification for AVMs†	
1	12/110 (10.9%)
2	44/110 (40.0%)
3	47/110 (42.7%)
4	7/110 (6.4%)
Affected tissue types	
Cutaneous	55/114 (48.2%)
Subcutaneous	88/114 (77.2%)
Intramuscular	67/114 (58.8%)
Osseous	16/114 (14.0%)
Parenchymatous	2/114 (1.8%)
AVM involving one tissue type	35/114 (30.7%)
AVM involving several tissue types	79/114 (69.3%)
Extension into central nervous system	
Yes	6/114 (5.3%)
No	108/114 (94.7%)
Distribution according to ISSVA‡ classification 2025	
Isolated	74/114 (64.9%)
Multifocal	13/114 (11.4%)
Syndromic	27/114 (23.7%)
Accompanying hypertrophy	
Yes	53/114 (46.5%)
Soft tissue	41/114 (36.0%)
Bone	1/114 (0.9%)
Both	11/114 (9.6%)
No	61/114 (53.5%)

* Cho classification according to Cho, Do [12] †Schobinger classification according to Kohout, et al. [11]. ‡ISSVA classification of vascular anomalies ©2025 international society for the study of vascular anomalies available at "issva.org/classification"

Table 2 Treatment course and follow-up

	Total cohort
Treatment	
None	12/114 (10.5%)
Yes	102/114 (89.5%)
IR ⁺ only	49/114 (43.0%)
IR ⁺ and surgery	23/114 (20.2%)
IR ⁺ and targeted medical therapy	11/114 (9.6%)
Surgery only	6/114 (5.3%)
IR ⁺ , surgery, and targeted medical therapy	6/114 (5.3%)
Targeted medical therapy only	3/114 (2.6%)
IR ⁺ and laser	3/114 (2.6%)
Laser only	1/114 (0.9%)
Type of targeted medical therapy	20/114 (17.5%)
Trametinib only	6/114 (5.3%)
Sirolimus only	5/114 (4.4%)
Thalidomide only	3/114 (2.6%)
Trametinib and Thalidomide	2/114 (1.8%)
Bevacizumab only	1/114 (0.9%)
Dabrafenib only	1/114 (0.9%)
Bevacizumab and Trametinib	1/114 (0.9%)
Lenalidomide and Trametinib	1/114 (0.9%)
Number of invasive treatment session, median (range)	3 (0–41)
Treatment response at last follow-up	
Complete regression	14/83 (16.9%)*
Partial regression	50/83 (60.2%)
Stable	14/83 (16.9%)
Progression	5/83 (6.0%)
Relapse during treatment course	
Yes	32/76 (42.1%)
Management adapted by genetic findings	43/114 (37.7%)
Targeted medical therapy	12/114 (10.5%)
Impact on family counseling	18/114 (15.8%)
Revision of the clinically suspected diagnosis	13/114 (11.4%)

+ IR Interventional radiology, e.g. embolization. *Including three cases of surgical amputation

unsolved, further divided into methodological unrestricted in 7/13 (53.8%; 6.0% of total cohort) and restricted in 6/13 (46.2%; 5.3% of total cohort) cases. The detailed methodological limitations that may explain the absence of detectable variants in the latter group can be found in Table 3. In three of 114 (2.6%) cases the genetic analysis was not feasible due to insufficient DNA quality from FFPE samples (Table 3).

The identified PVs involved the genes *KRAS* in 24/114 (21.1%, Fig. 2), *MAP2K1* in 20/114 (17.5%), *HRAS* in 10/114 (8.8%), and *BRAF* in 9/114 (7.9%, Fig. 3) patients. Eight of 114 (7.0%) patients carried a germline *RASAI* variant, while two (2/114, 1.8%) patients harbored a somatic pathogenic *RASAI* variant. Six

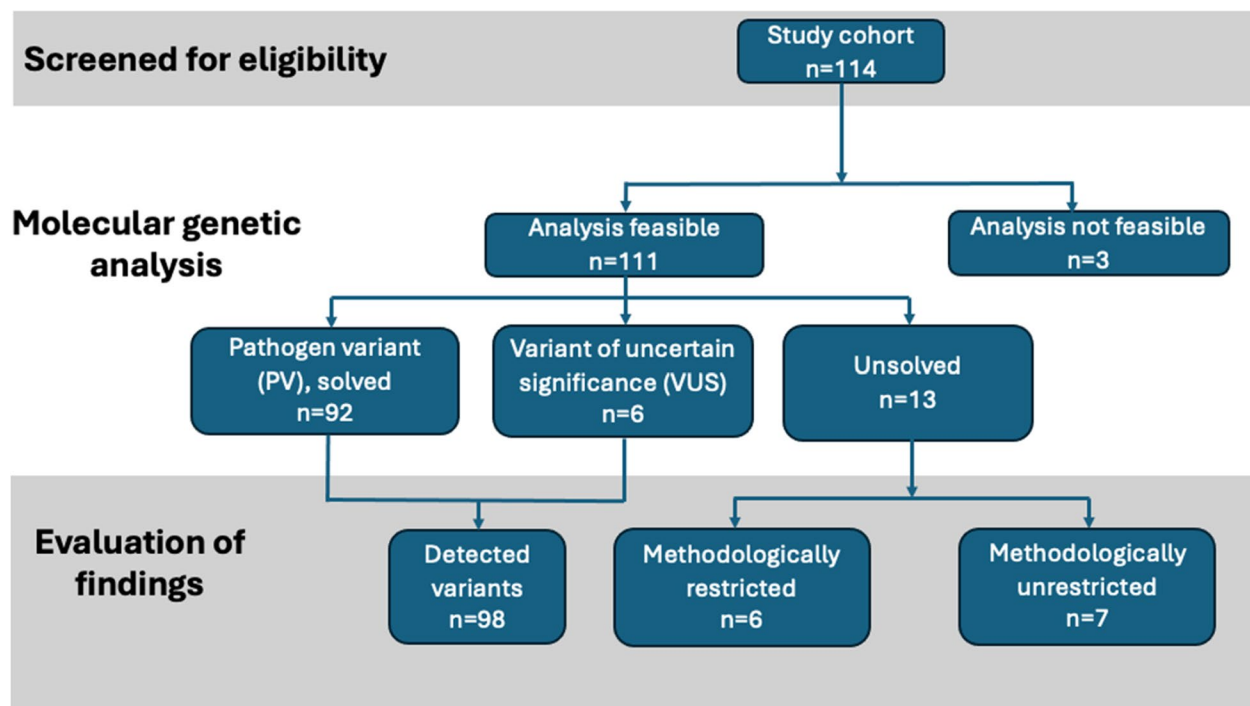


Fig. 1 Consort flow chart presenting AVM cohort size and variant detection rate

Table 3 Molecular genetic analysis and detection rate of PVs

	Total cohort
Molecular genetic analysis	114/114 (100%)
Testing not feasible	3/114 (2.6%)
FFPE without interpretable result*	1/114 (0.9%)
Sanger sequencing on FFPE DNA only*	1/114 (0.9%)
FFPE with 166× coverage, repeated analysis with 184× coverage only	1/114 (0.9%)
Testing feasible	111/114 (97.4%)
Total detection rate	98/114 (86.0%)
Pathogenic variants (PVs), solved	92/114 (80.7%)
Variants of uncertain significance (VUS)	6/114 (5.3%)
Unsolved cases	13/114 (11.4%)
Methodological unrestricted	7/114 (6.1%)
Methodological restricted	6/114 (5.3%)
cfDNA only	2/114 (1.8%)
Germline testing only (EDTA-blood)	2/114 (1.8%)
Limited gene panel	1/114 (0.9%)

cfDNA circulating-free deoxyribonucleic acid, EDTA ethylenediaminetetraacetic acid, FFPE Formalin-fixed, paraffin-embedded. *No adequate material for repeated analyses

of 114 (5.3%) patients were found to have a germline *PTEN* variant and three 3/114 (2.6%) patients a somatic pathogenic *PTEN* variant. Germline *EBH4* variants were observed in 4/114 (3.5%), identically in number to

PIK3CA somatic variants (4/114, 3.5%). A somatic PV in *SOS1* was detected in 3/114 (2.6%) cases, followed by two *GNAQ* PVs (2/114, 1.8%) as well as one *RIT1* PV, one *RAF1* VUS, and one *GNA14* PV (each 1/114, 0.9%, Fig. 4). Variant allele frequencies (VAFs) in DNA from lesional tissue samples ranged from 0.3% to 23.0% (Additional file 2: Table 2) with VAFs < 1.0% in 3/114 cases (2.6%) and VAFs < 3.0% in 12/114 cases (10.5%).

Together gene variants in *KRAS*, *HRAS*, *BRAF*, and *MAP2K1* accounted for 55.3% of cases overall (63/114) and 78.8% of cases with somatic variants (63/80). While *KRAS*, *BRAF*, and *MAP2K1* variants predominantly involved the mutational hotspots for oncogenic variants at codons 12 and 61 (*KRAS*), 600 (*BRAF*), and 56/57 (*MAP2K1*), *HRAS* PVs were exclusively indels affecting the switch 2 region of the protein. This observation is in line with previous reports [13, 14].

Genotype–phenotype associations

When comparing between cases with PVs in the *RAS*, *MAP2K1*, and *BRAF* genes, the *RAS* group showed a more severe clinical stage according to Schobinger (stage 2 in *RAS*: 65.6% vs. 40.0% and 37.5% in *MAP2K1* and *BRAF*, $p=0.027$) and a higher relapse rate (55.6% in *RAS* vs. 43.8% and 0.0% in *MAP2K1* and *BRAF*, $p=0.049$). Potential confounders did not show a significant effect on Schobinger stage (multinomial regression; age:

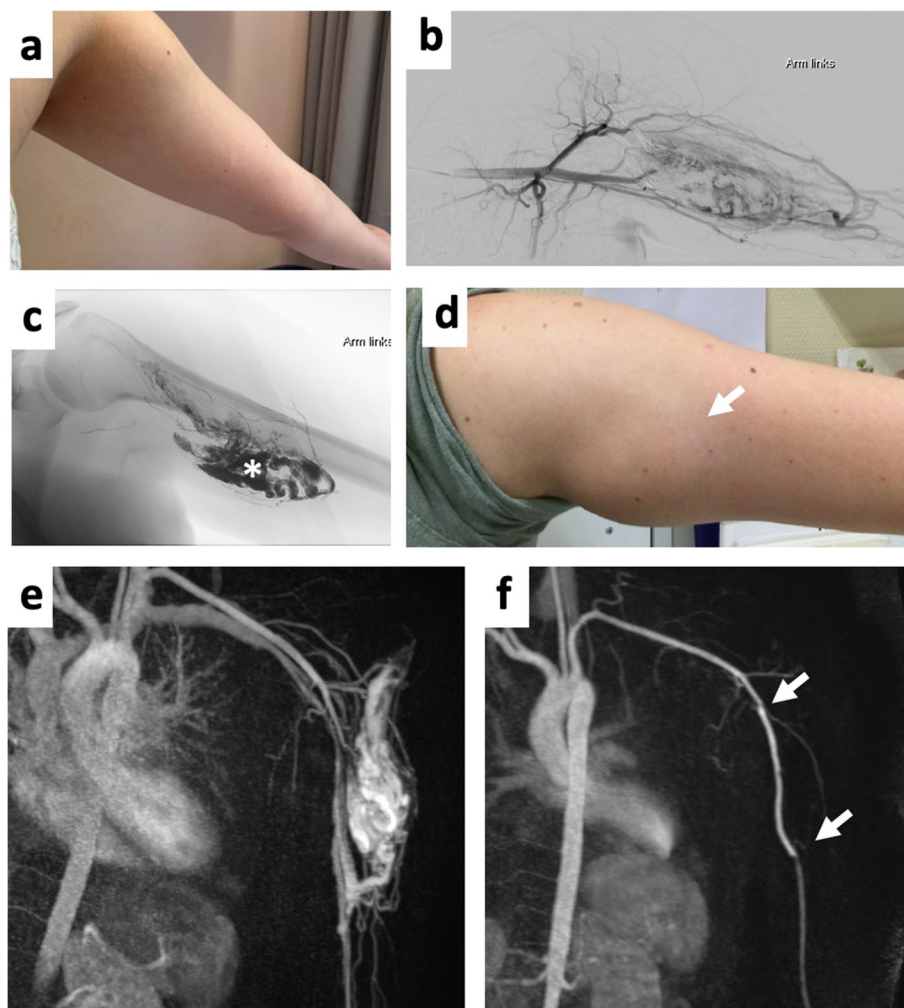


Fig. 2 (Pat. No. 8). 27-year-old female patient with an arteriovenous malformation (AVM) of the left upper arm and a KRAS pathogenic variant. **a** Clinical presentation of the AVM after two prior embolization procedures (**a**), **b**, **c** Digital subtraction angiography (DSA) images presenting the angioarchitecture of the lesion and the remaining liquid embolization material (asterisk). **d** Clinical presentation of the AVM at clinical relapse with a clearly visible increase in size compared to (**a**), observed after an interval of 5 months (**b**, arrow). **e**. Time-resolved angiography with interleaved stochastic trajectories angiography (TWIST) magnetic resonance angiography (MRA) image showing the marked hyperperfusion and newly vascularized components of the progressive AVM. **f** TWIST MRA image after surgical resection of the AVM, including removal of the long head of the biceps and vascular and nerve dissection. Due to involvement of the brachial artery, a venous interposition graft from the right thigh was performed to restore and maintain blood flow to the arm (arrows)

OR=1.03; 95% CI: 0.93–1.14; $p=0.599$; sex: OR=2.32; 95% CI: 0.16–34.03; $p=0.540$) or on the occurrence of relapse (binary regression model; age: OR=1.01; 95% CI: 0.96–1.05; $p=0.820$; sex: OR=1.43; 95% CI: 0.40–5.09; $p=0.586$; treatment method: OR=1.08; 95% CI: 0.78–1.49; $p=0.658$). Regarding the tissue involvement, AVMs with *BRAF* variants involved a single tissue type in 44.4% compared to *RAS* in 32.4% and *MAP2K1* in 35.0%, though this was not statistically significant. No remarkable differences were observed in the prevalence of clinical manifestations, such as anatomical lesion localization,

accompanied hypertrophy, or in the angiographic classification according to Cho (all $p>0.05$, Table 4).

When comparing germline and mosaic variants, we found no relevant association with clinical stages according to Schobinger ($p=0.355$), angiographic classification according to Cho ($p=0.950$), or recurrence rate ($p=0.940$). As expected, the assessed distribution pattern showed significant differences between the two groups, with more syndromic patterns in germline variants (61.1% vs. 15.6%, $p<0.001$). AVMs due to germline mutations trended to involve more frequently two or more

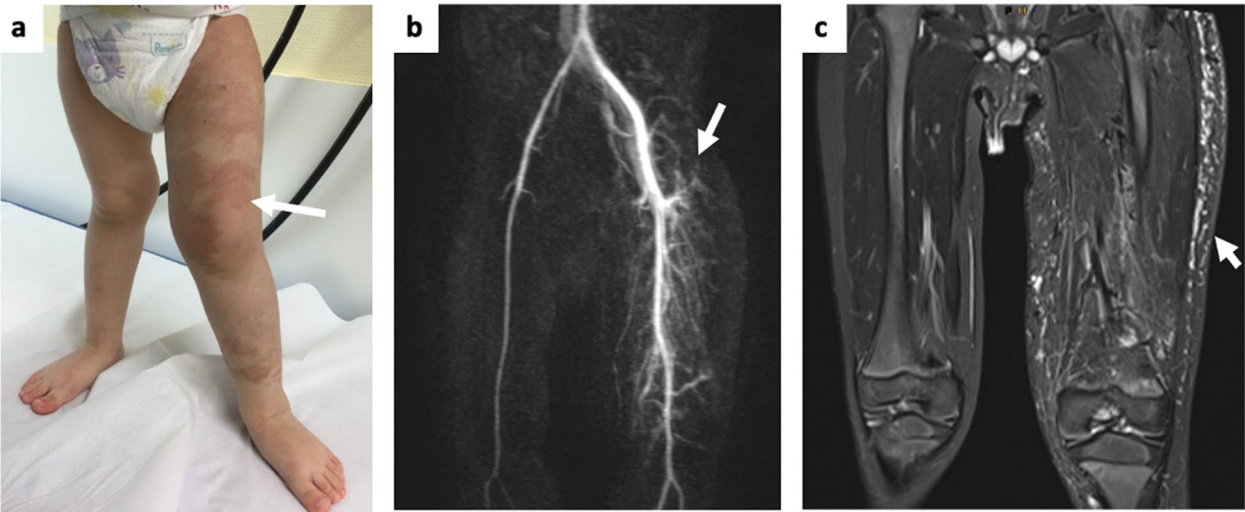


Fig. 3 (Pat. No. 57). 2-year-old male patient presenting with a Parkes Weber syndrome-like phenotype of the left leg and somatic *BRAF* pathogenic variant. **a** Clinical presentation of the affected left leg with soft tissue hypertrophy of the thigh and confluent capillary malformations (arrow) with noticeable hyperthermia; furthermore, leg lengths discrepancy (left > right, 2 cm) was observed. **b** Time-resolved angiography with interleaved stochastic trajectories (TWIST) magnetic resonance angiography (MRA) image showing fine-fistulous AVM-components of the left thigh (arrow). **c**. T2-weighted turbo spin echo (TSE) MR image presenting the extent of the AVM components and accompanied soft tissue hypertrophy and edema (arrow)

Results of molecular genetic analysis

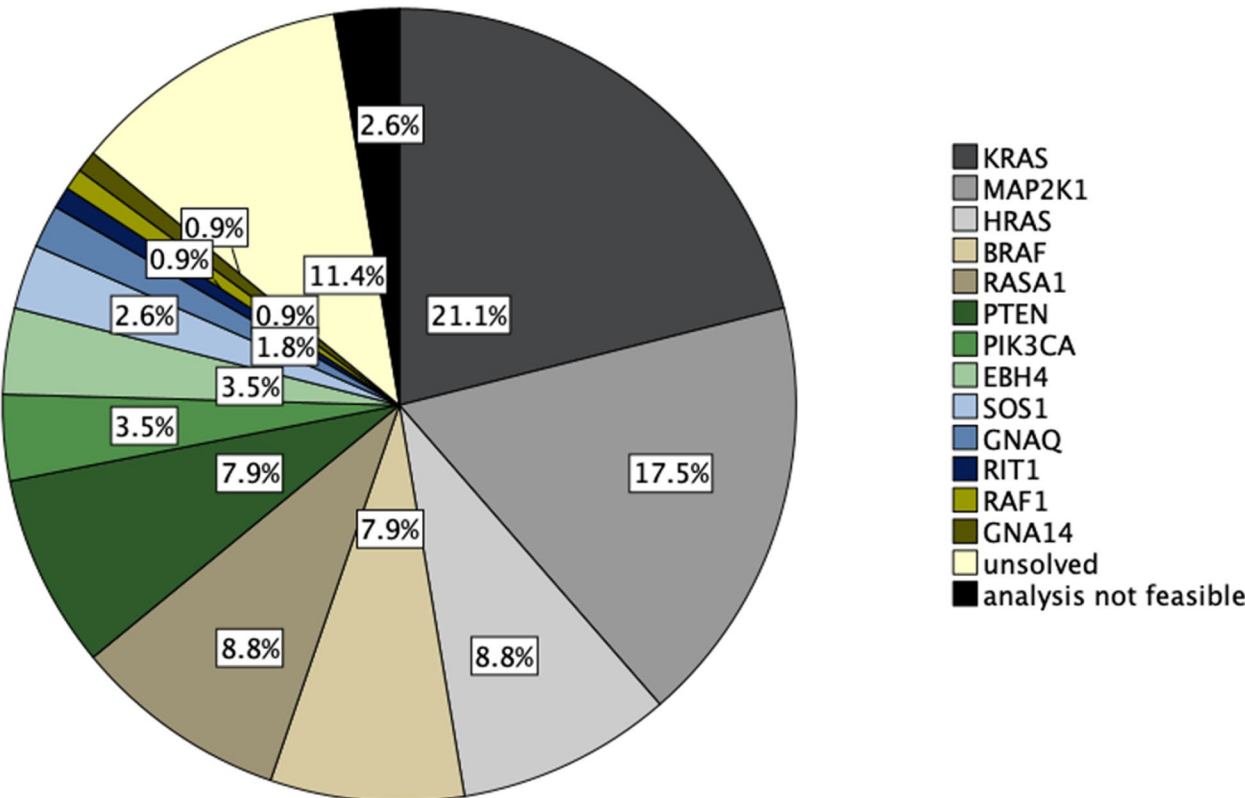


Fig. 4 Results of molecular genetic analysis and variant spectrum in AVM cohort

Table 4 Comparison of clinical characteristics between PVs of RAS/MAPK-pathway

Clinical characteristics	RAS	BRAF	MAP2K1	p-value
<i>Lesion localization</i>				$p = 0.301^{\#}$
Lower Extremity	15/34 (44.1%)	4/9 (44.4%)	5/20 (25.0%)	
Head and neck	8/34 (23.5%)	2/9 (22.2%)	9/20 (45.0%)	
Upper extremity	5/34 (14.7%)	0/9 (0.0%)	3/20 (15.0%)	
Trunk	4/34 (11.8%)	1/9 (11.1%)	1/20 (5.0%)	
Extensive lesions (two or more anatomical regions)	2/34 (5.9%)	2/9 (22.2%)	2/20 (10.0%)	
<i>Cho classification for AVMs*</i>				$p = 0.817^{\#}$
I	1/31 (3.2%)	0/7 (0.0%)	0/17 (0.0%)	
II	3/31 (9.7%)	0/7 (0.0%)	0/17 (0.0%)	
IIIa	13/31 (41.9%)	4/7 (57.1%)	7/17 (41.2%)	
IIIb	14/31 (45.2%)	3/7 (42.9%)	10/17 (58.8%)	
<i>Schobinger classification for AVMs†</i>				$p = 0.027^{\#}$
1	0/32 (0.0%)	3/8 (37.5%)	2/20 (10.0%)	
2	10/32 (31.2%)	2/8 (25.0%)	8/20 (40.0%)	
3	21/32 (65.6%)	3/8 (37.5%)	8/20 (40.0%)	
4	1/32 (3.1%)	0/8 (0.0%)	2/20 (10.0%)	
<i>Involvement of tissue types</i>				$p = 0.795^{\dagger}$
One tissue type	11/34 (32.4%)	4/9 (44.4%)	7/20 (35.0%)	
Several tissue types	23/34 (67.6%)	5/9 (55.6%)	13/20 (65.0%)	
<i>Distribution according to ISSVA 2025 classification‡</i>				$p < 0.341^{\#}$
Isolated	23/34 (67.6%)	7/9 (77.8%)	18/20 (90.0%)	
Multifocal	1/34 (2.9%)	1/9 (1.1%)	1/20 (5.0%)	
Syndromic	8/34 (23.5%)	1/9 (1.1%)	1/20 (5.0%)	
<i>Accompanied hypertrophy</i>				$p = 0.641^{\dagger}$
yes	16/34 (47.1%)	3/9 (33.3%)	7/20 (35.0%)	
no	18/34 (52.9%)	6/9 (66.7%)	13/20 (65.0%)	
<i>Relapse during medical/invasive treatment</i>				$p = 0.049^{\dagger}$
Yes	10/18 (55.6%)	0/6 (0.0%)	7/16 (43.8%)	
No	8/18 (44.4%)	6/6 (100.0%)	9/16 (56.3%)	

* Cho classification according to Cho, Do [12]; † Schobinger classification according to Kohout et al. [11]. ‡ Chi-square test. # Fisher's exact test if $n < 5$ in $> 20\%$ of cell counts. † ISSVA classification of vascular anomalies ©2025 international society for the study of vascular anomalies available at "issva.org/classification"

anatomical regions, although not statistically significant (27.8% vs. 10.4%, $p = 0.08$; Table 5).

No differences were observed between the detected variants and the unsolved cases when comparing clinical characteristics (all $p > 0.05$, Table 6).

Discussion

This retrospective multicenter study examined the detection rate and mutational landscape of PVs in AVMs and explored correlations between clinical characteristics and the implicated genes and variants. The diagnostic yield was high with variants detected in 86% of the cohort (80.7% PVs, 5.3% VUS). Most detected variants clustered within the RAS/MAPK signaling cascade, although the overall spectrum was broad containing 13 genes, both mosaic and germline variants, including not yet described variants. Syndromic distribution patterns were more frequent in germline variants than in mosaic

variants, whereas no differences were observed for other clinical characteristics. Lesions with RAS PVs showed more advanced disease stages and higher relapse rates compared to MAP2K1 and BRAF PVs in line with other publications.

This study's genetic detection rate of 86.0%, encompassing both PVs and VUS, is higher than reported in the AVM literature. This was further supported by the fact that only 6% of AVM cases remained unrestricted—unsolved, despite having undergone the maximum available genetic work-up with the current methodological possibilities. In 2018, Al-Olabi et al. identified somatic mosaic activating variants in the RAS/MAPK pathway (KRAS, BRAF, MAP2K1) in 6 of 9 patients (67%) using targeted NGS, thus they were among the first to establish these mutations as major drivers of sporadic AVMs [15]. A study by Green et al. identified somatic variants in KRAS and MAP2K1 in 36% of 11

Table 5 Comparison of clinical characteristics between germline and mosaic variants

Clinical characteristics	Germline variants	Mosaic variants	p-value
<i>Lesion localization</i>			$p=0.080^{\#}$
Lower Extremity	8/18 (44.4%)	35/96 (36.5%)	
Head and neck	3/18 (16.7%)	30/96 (31.3%)	
Upper extremity	1/18 (5.6%)	13/96 (13.5%)	
Trunk	0/18 (0.0%)	7/96 (7.3%)	
Parenchymatous organs	1/18 (5.6%)	1/96 (5.6%)	
Extensive lesions (two or more anatomical regions)	5/18 (27.8%)	10/96 (10.4%)	
<i>Cho classification for AVMs*</i>			$p=0.950^{\#}$
I	0/12 (0.0%)	2/84 (2.4%)	
II	1/12 (8.3%)	7/84 (8.3%)	
IIIa	4/12 (33.3%)	33/84 (39.3%)	
IIIb	7/12 (58.3%)	42/84 (50.0%)	
<i>Schobinger classification for AVMs†</i>			$p=0.355^{\#}$
1	3/18 (16.7%)	9/92 (9.8%)	
2	8/18 (44.4%)	36/92 (39.1%)	
3	5/18 (27.8%)	42/92 (45.7%)	
4	2/18 (11.1%)	5/92 (5.4%)	
<i>Involvement of tissue types</i>			$p=0.395^{\ddagger}$
One tissue type	4/18 (22.2%)	31/96 (32.3%)	
Several tissue types	14/18 (77.8%)	65/96 (67.7%)	
<i>Distribution according to ISSVA 2025 classification‡</i>			$p<0.001^{\#}$
Isolated	3/18 (16.7%)	71/96 (73.9%)	
Multifocal	4/18 (22.2%)	9/96 (9.4%)	
Syndromic	11/18 (61.1%)	16/96 (16.7%)	
<i>Accompanied hypertrophy</i>			$p=0.205^{\#}$
yes	11/18 (61.1%)	42/96 (43.8%)	
no	7/18 (38.9%)	54/96 (56.3%)	
<i>Relapse during medical/invasive treatment</i>			$p=0.940^{\ddagger}$
Yes	7/12 (58.3%)	32/56 (57.1%)	
No	5/12 (41.7%)	24/56 (42.9%)	

* Cho classification according to Cho, Do [12]; †Schobinger classification according to Kohout et al. [11]. ‡Chi-square test. #Fisher's exact test if $n < 5$ in $> 20\%$ of cell counts. ‡ISSVA classification of vascular anomalies ©2025 international society for the study of vascular anomalies available at "issva.org/classification"

individuals with AVMs thereby using a broad approach with multiple methods including droplet digital PCR, Sanger sequencing, and high-depth exome sequencing [16]. El Sissy et al. identified PVs in 23.6% of blood samples drawn from 55 patients with AVMs, predominantly in *MAP2K1* and *KRAS* genes, with higher sensitivity near the AVM nidus [17]; this lower detection rate may be attributed to relevant methodological differences, as liquid biopsies applied cfDNA analysis, with lower sensitivity compared to tissue biopsies. Hernandez et al. reported 37 out of 54 patients (68.5%) with identified PVs, while 3.7% had VUS and 27.8% had negative results [18]. Their reported variant spectrum was predominantly composed of *MAP2K1* (12 cases), *KRAS* (8 cases), and *TEK* (7 cases), with some cases also harboring germline variants in *PTEN* and *RASA1* [18]. In comparison, no *TEK* PVs were detected in any AVM of

this cohort, but *TEK* is generally known to be involved in sporadic venous malformations [19]. A recent systematic review on genetic mutations included 69 studies across all type of vascular malformations reporting a causative variant in 40% of cases [20]. Overall, the high diagnostic yield in our study is likely attributable to the systematic use of high-sensitivity ultra-deep sequencing, with continuously evolving panels for somatic, germline, and combined analysis. Furthermore, enhanced quality of the tissue samples in our cohort may be attributable to the fact that the biopsies were deliberately taken as centrally as possible within the AVMs. In addition, the detection rate may have been influenced by cohort characteristics; for example, multifocal capillary malformation–AVM (CM-AVM) cases show a higher rate of *RASA1* variants, with up to 70% of cases carrying a detectable mutation [21].

Table 6 Comparison of clinical characteristics between unsolved cases and detected variants

Clinical characteristics	Unsolved cases	Detected variants ^{##}	p-value
<i>Lesion localization</i>			p = 0.140 [#]
Lower Extremity	3/13 (23.1%)	36/92 (39.1%)	
Head and neck	3/13 (23.1%)	26/92 (28.3%)	
Upper extremity	4/13 (30.8%)	9/92 (9.8%)	
Trunk	0/13 (0.0%)	7/92 (7.6%)	
Parenchymatous organs	1/13 (7.7%)	1/92 (1.1%)	
Extensive lesions (two or more anatomical regions)	2/13 (15.4%)	13/92 (14.1%)	
<i>Cho classification for AVMs[*]</i>			p = 0.166 [#]
I	1/11 (9.1%)	1/76 (1.3%)	
II	1/11 (9.1%)	4/76 (5.3%)	
IIIa	3/11 (27.3%)	31/76 (40.8%)	
IIIb	6/11 (54.5%)	40/76 (52.6%)	
<i>Schobinger classification for AVMs[†]</i>			p = 0.889 [#]
1	2/12 (16.7%)	10/89 (11.2%)	
2	4/12 (33.3%)	34/89 (38.2%)	
3	5/12 (41.7%)	39/89 (43.8%)	
4	1/12 (8.3%)	6/89 (6.7%)	
<i>Involvement of tissue types</i>			p = 1.000 [‡]
One tissue type	4/13 (30.8%)	29/92 (46.8%)	
Several tissue types	9/13 (69.2%)	63/92 (68.5%)	
<i>Distribution according to ISSVA 2025 classification[‡]</i>			p = 0.740 [#]
Isolated	9/13 (69.2%)	58/92 (63.0%)	
Multifocal	2/13 (15.4%)	10/92 (10.9%)	
Syndromic	2/13 (15.4%)	24/92 (26.1%)	
<i>Accompanied hypertrophy</i>			p = 1.000 [‡]
yes	6/13 (46.2%)	42/92 (45.7%)	
no	7/13 (53.8%)	50/92 (54.3%)	
<i>Relapse during medical/invasive treatment</i>			p = 0.714 [#]
Yes	4/8 (50.0%)	34/58 (58.6%)	
No	4/8 (50.0%)	24/58 (41.4%)	

^{*} Cho classification according to Cho, Do [12]; [†] Schobinger classification according to Kohout et al. [11]. [‡] Chi-square test. [#] Fisher's exact test if n < 5 in > 20% of cell counts. [‡] ISSVA classification of vascular anomalies ©2025 international society for the study of vascular anomalies available at "issva.org/classification". ^{##} Detected variants include both pathogenic variants (PVs, solved cases) and variants of unknown significance (VUS)

In this AVM cohort, mosaic or germline variants were identified in 13 different genes, representing a broad spectrum that also included some genes rarely reported in the context of AVMs, as well as novel genes. Compared to existing literature, we similarly observed a predominance of genes from the RAS/MAPK signaling pathway, primarily driven by *KRAS* and *MAP2K1*; however, we also noted a relevant proportion of *HRAS* (8.8%) and *BRAF* (7.9%) cases. In contrast, in the meta-analysis of Stor et al., only six and seven of 1,686 patients carried an activating somatic *HRAS* and *BRAF* variant, respectively. Variant calling of larger indels in *HRAS* cases may have been less efficient in preceding publications, potentially leading to missed variants. A similar rate of *BRAF* PVs of 8.7% was reported in the

study by El Sissy et al. analyzing 23 AVM tissue samples [22]. Since *BRAF* cases have been generally described less frequently, less is known about this phenotype [23]. Our data indicate that these AVMs presented with lower disease stages and, in our cohort, showed no relapses in any of the affected patients (0%), despite also exhibiting complex angiographic phenotypes according to the Cho classification. In contrast, AVMs with PVs in *RAS* genes showed a higher relapse rate (55.6%) and more advanced disease stages. This pattern, representing a phenotype of primarily extensive and progressive AVMs, has also been previously reported by Stor et al. and Schmidt et al. [5, 20]. Overall, these data suggest that AVMs harboring a somatic RAS variant are associated with more advanced disease stages and higher

relapse rates, indicating a need for further studies to determine optimal management strategies.

Yet, when interpreting the results it needs to be considered that patients in this cohort received various treatments, from minimal-invasive, open surgery to targeted pharmacological treatments. Statistically the treatment method itself did not represent a confounding factor for disease relapse. However, it has been shown that the treatment modality can potentially influence both the occurrence and the time to onset of relapse, for example embolization alone was reported to being associated with earlier recurrence compared to embolization plus resection [24, 25]. With respect to both disease stage and recurrence rate, AVMs with *MAP2K1* variants fell between *BRAF* and *RAS*, showing advanced stages and a relevant relapse rate (43.8%), but to a lesser extent than *RAS*. While AVMs with *RAS* variants commonly exhibited syndromic distribution patterns, *MAP2K1* AVMs were mostly found as isolated lesions, in line with prior reports [22].

PVs/VUS in *RASA1* and *PTEN* were predominantly found as germline variants in this cohort (8/10 and 6/9, respectively). The 8 germline cases and one of the two somatic *RASA1* cases presented with the typical phenotype of CM-AVM syndrome, with extensive, multifocal capillary malformations and associated AVMs, comparable to most reports of *RASA1* cases in literature [21, 26]. However, the remaining somatic *RASA1* case presented with an isolated AVM located in the palate. AVMs with *PTEN* variants were found in the lower extremities in 7 of 9 cases, and both germline and somatic *PTEN* variants exhibited intramuscular AVM components and surrounding hamartomatous changes. As part of the *PTEN*-hamartoma syndrome, these patients may not only present with vascular malformations but also with additional associated anomalies such as macrocephaly and multiple intracranial DVAs [27]. In addition to the germline variants in *RASA1* and *PTEN*, there were four germline variants in the *EPHB4* gene. Regarding the *EPHB4* cases, three were associated with capillary malformations, consistent with previous reports [28], whereas one case presented as an isolated parenchymal intra-abdominal AVM. As expected, comparison between germline and somatic variants revealed differences in distribution patterns of vascular lesions: germline variants were predominantly associated with syndromic patterns and tended to involve more tissue layers. In line with this, Valdivielso-Ramos et al. [29] reported that germline *RASA1*-positive patients were more likely than *RASA1*-negative patients to present with a higher total number of clinical lesions, while Chen et al. demonstrated that germline pathogenic *RASA1* variants were associated with a higher risk of multifocal CM compared to somatic

variants [30]. No differences were observed in other clinical parameters, including angiographic findings, clinical classification, or relapse rates. These findings suggest that clinical presentation alone does not allow for a reliable distinction between germline and somatic mutations. Further, there is currently no evidence-based indication that germline PVs should be treated more intensively or proactively than somatic PVs.

PIK3CA variants were detectable in a small subset of this cohort including one VUS. The low percentage of *PIK3CA* variants in this study is consistent with previously described genetic spectra in AVMs. In general, *PIK3CA* is more associated with slow-flow vascular malformations and *PIK3CA*-related overgrowth spectrum diseases, and clinical presentations are highly variable, ranging from solitary lesions to syndromic forms with hypertrophy and non-vascular anomalies [20]. Two *GNAQ* PVs (p.Arg183Gln) were found in this study, one of which presented with a Sturge-Weber syndrome like phenotype fitting with prior reports [31], but with an unexpectedly fast flow in the lesion. The remaining *GNAQ* case in our cohort presented with extensive infiltrative AVM of the head and neck, notably due to a *GNAQ* p.Gln209His mutation, which is a more aggressive *GNAQ* mutation often found in uveal melanoma. The one AVM patient with a confirmed *GNAI4* PV presented with a head and neck AVM with components also involving the central nervous system. This variant has been only reported in a single case that harbored both a *PIK3CA* and a *GNAI4* PV [32]. PVs in *SOS1* and a VUS in *RAF1* were identified in three and one patients, respectively. These genes have not yet been directly associated with AVMs, but are reported to be present in 3–20% in Noonan syndrome [33, 34]. *SOS1* activates RAS proteins while *RAF1* functions downstream of RAS and upstream of MEK1/2, and thus both represent components of the canonical RAS/MAPK signaling pathway. In one AVM, a *RIT1* PV was found, this case was previously published and *RIT1* was functionally characterized as novel gene implicated in the pathogenesis of AVMs [35]. As PVs in *SOS1*, *RAF1*, and *RIT1* genes present the capacity to hyperactivate the RAS-MAPK pathway, MEK inhibitors such as trametinib appear as medical targeted therapy option, which have already been used experimentally in individual cases [35]. In this cohort, one patient with a *SOS1* PV and the patient with a *RIT1* PV were treated successfully with trametinib. Overall, targeted medical therapy was initiated in 12.2% of the cases with detected variants following the genetic diagnosis. Patients treated with targeted therapy represent a relevant part of the 43 patients in this cohort whose clinical management was directly influenced by the genetic findings. Other patients were directed for family counseling or their diagnosis

was revised due to the genetic finding. Similar observations including genetics-driven targeted therapy in 43 of 69 patients with vascular anomalies were reported by Li et al. [14].

Since no relevant differences in clinical characteristics were observed between AVMs with detected variants and those that remained unsolved, there currently is no rationale for pursuing a different therapeutic approach in AVMs without any identifiable underlying mutation. It can be anticipated that the proportion of unsolved cases will continue to decline, due to increasingly sensitive methods that allow the detection of very low VAFs in tissue samples, due to the identification of additional causative genes and due to further refinement of optimal material acquisition for genetic testing.

The limitations of this study include its retrospective design and the multicenter setting which may restrict available data (e.g. exact time point of relapse) as well as introduce inter-center heterogeneity in patient selection, diagnostic work-up, and treatment strategies, potentially affecting data consistency. Comparisons between subgroups were limited by the small and variable group sizes across individual PVs and VUS. Despite these limitations, this AVM study, retrieved robust molecular genetic findings in a real-world setting with substantial clinical implications, which may be further validated and expanded in future prospective studies.

Conclusions

In this study, PVs and VUS have been detected in the majority of cases, predominantly within the RAS/MAPK pathway. Somatic *RAS* PVs correlated with advanced disease stages and higher relapse rates compared to *MAP2K1* and *BRAF* PVs, while germline variants were more often associated with syndromic patterns. Rare somatic variants in genes such as *SOS1*, *RAF1*, and *RIT1* were also identified, highlighting the expanding spectrum of contributors to AVM pathogenesis and allowing targeted medical therapy.

Abbreviations

AKT	Protein kinase B
AVM	Arteriovenous malformation
BRAF	V-Raf murine sarcoma viral oncogene homolog B
cfDNA	Circulating cell-free deoxyribonucleic acid
CM	Capillary malformation
EBHB4	Ephrin-receptor B4
EDTA	Ethylenediaminetetraacetic acid
FFPE	Formalin-fixed, paraffin-embedded
GAP	GTPase-activating protein
GNA14	G protein subunit alpha 14
GNAQ	Guanine nucleotide-binding protein G(q) subunit alpha
GTP	Guanosine triphosphate
HRAS	Harvey rat sarcoma viral oncogene homolog
ISSVA	International society for the study of vascular anomalies
KRAS	Kirsten rat sarcoma viral oncogene
LPATH	Likely pathogenic
MAPK	Mitogen-activated protein kinase

MAP2K1	Mitogen-activated protein kinase kinase 1
mtor	Mammalian target of rapamycin
NRAS	Neuroblastoma ras viral oncogene homolog
PATH	Pathogenic
PI3K	Phosphatidylinositol-3-kinase
PIK3C	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PV	(Likely) Pathogenic variant
RAF1	Raf-1 proto-oncogene, serine/threonine kinase
RASA1	RAS p21 protein activator 1
RIT1	Ras like without CAAX 1
PTEN	Phosphatase and tensin homolog
SOS1	Son of sevenless homolog 1
STREGA	Strengthening the reporting of genetic association studies
TIRM	Turbo-inversion-recovery-magnitude
TSE	Turbo-spin-echo
TWIST	Time-resolved-angiography-with-interleaved-stochastic-trajectories
VUS	Variant of uncertain significance

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-026-04874-0>.

Additional file 1. Table 1 Strengthening the Reporting of Genetic Association Studies (STREGA) guidelines.

Additional file 2. Table 2 Mutational spectrum and genotypic characterization of study cohort.

Additional file 3. Details about DNA extraction, variant screening, and genetic analysis.

Additional file 4. Table 3 Custom panel gene content.

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Authors' contributions

Conceptualization was contributed by VFS, DS, MZ, MW, and FGK. VFS appears first in the author list because of her involvement in the initiation of the project due to project-related intramural funding. Vascular anomalies were clinically and radiologically diagnosed and/or treated by VFS, RB, JHL, WU, MD, ÖC, SH, VV, MP, FO, MS1, AS, DP, SD, JBWW, BH, AH, AF, JH, AH, PBS, TS, JR, SL, MS2, WAW, MZ, MW, and FGK. Targeted sequencing of panels of genes was performed by DS, TS, and MZ. Investigation was contributed by VFS, MAK, MW, and FGK. Writing of the original draft was contributed by VFS, DS, MZ, MW, and FGK. All authors read and approved the final manuscript.

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Data availability

Detailed mutational spectra and genotypic characterization of the study cohort are provided in Additional file 2: Table 2. Due to privacy restrictions protecting study participants, the clinical datasets analyzed during the current study are not publicly available but may be obtained from the corresponding author upon reasonable request (vanessa.schmidt@med.uni-muenchen.de). Requests will generally be processed within 4 weeks.

Declarations

Ethics approval and consent to participate

Retrospective analyses were approved by the local ethics committee (University Hospital, LMU Munich, protocol no: 23–0337).

Consent for publication

All patients/legal representatives shown in the figures provided written informed consent for the use and publication of scientific data, radiological images and clinical photographs, including open access format/creative commons licence for scientific purpose.

Competing interests

Authors JBWW and FGK received consultation fees from Novartis. All other authors declare that they have no competing interests.

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