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Capillary Malformation-Arteriovenous Malformation Syndrome

Synonym: CM-AVM Syndrome

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Summary

Clinical characteristics

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is characterized by the presence of multiple small (1-2 cm in diameter) capillary malformations mostly localized on the face and limbs. Some affected individuals also have associated arteriovenous malformations (AVMs) and/or arteriovenous fistulas (AFVs), fast-flow vascular anomalies that typically arise in the skin, muscle, bone, spine, and brain; life-threatening complications of these lesions can include bleeding, congestive heart failure, and/or neurologic consequences. Symptoms from intracranial AVMs/AVFs appear to occur early in life. Several individuals have Parkes Weber syndrome (multiple micro-AVFs associated with a cutaneous capillary stain and excessive soft-tissue and skeletal growth of an affected limb).

Diagnosis/testing

The diagnosis of CM-AVM syndrome is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *EPHB4* or *RASA1* identified by molecular genetic testing.

Management

Treatment of manifestations: For capillary malformations and telangiectases that are of cosmetic concern, referral to a dermatologist. For AVMs and AVFs, the risks and benefits of intervention (embolization vs surgery) must be considered, usually with input from a multidisciplinary team (e.g., specialists in interventional radiology, neurosurgery, surgery, cardiology, and dermatology). For cardiac overload, referral to a cardiologist. For hemihyperplasia and/or leg-length discrepancy, referral to an orthopedist. Lymphangiography to evaluate for lymphatic malformations may be considered; compression stockings for those with evidence of lymphedema; epistaxis treatment includes humidification, nasal lubricants, referral to otolaryngologist, and complete blood count for evaluation of anemia.

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Surveillance: Repeat imaging studies if clinical signs/symptoms of AVMs/AVFs become evident.

Evaluation of relatives at risk: Clarification of the genetic status of at-risk relatives is appropriate in order to allow early diagnosis and treatment of AVMs/AVFs to reduce/avoid secondary adverse outcomes.

Genetic counseling

CM-AVM syndrome is inherited in an autosomal dominant manner. For *RASA1*-CM-AVM syndrome, about 70% of affected individuals have an affected parent; about 30% have a *de novo* pathogenic variant. For *EPHB4*-CM-AVM syndrome, about 80% of affected individuals have an affected parent; about 20% have a *de novo* pathogenic variant. Each child of an individual with CM-AVM syndrome has a 50% chance of inheriting the pathogenic variant. Prenatal and preimplantation genetic testing are possible if the pathogenic variant has been identified in an affected family member.

GeneReview Scope

Capillary Malformation-Arteriovenous Malformation Syndrome: Additional Included Phenotype [1]
• *RASA1* Parkes Weber syndrome

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of this phenotype see Differential Diagnosis.

Diagnosis

Diagnostic criteria for capillary malformation-arteriovenous malformation (CM-AVM) syndrome have been proposed but not systematically evaluated [Orme et al 2013, Weitz et al 2015].

Suggestive Findings

CM-AVM syndrome **should be suspected** in probands who have **any** of the following:

- **Capillary malformations (CMs),** the hallmark of CM-AVM syndrome. CMs are generally:
  - Multifocal, atypical pink-to-reddish brown, multiple, small (1-2 cm in diameter), round-to-oval lesions sometimes with a white halo;
  - Composed of dilated capillaries in the papillary dermis [Hershkovitz et al 2008b];
  - Mostly localized on the face and limbs;
  - Seen in combination with arteriovenous malformations (AVMs) or arteriovenous fistulas (AVF), but may be the only finding [Hershkovitz et al 2008a, Revencu et al 2008, Revencu et al 2013b].
- **AVMs/AVFs** in soft tissue, bone, and brain that may be associated with overgrowth [Eerola et al 2003]
- **Parkes Weber syndrome phenotype,** a cutaneous capillary malformation associated with underlying multiple micro-AVFs and soft-tissue and skeletal hypertrophy of the affected limb [Mulliken & Young 1988]

Establishing the Diagnosis

The diagnosis of a CM-AVM syndrome **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *EPHB4* or *RASA1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section

is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *EPHB4* or *RASA1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of CM-AVM syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with capillary malformations and/or AVMs are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of CM-AVM syndrome, molecular genetic testing approaches can include use of a **multigene panel**. A multigene panel that includes *EPHB4*, *RASA1*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Note: (1) In *RASA1*-CM-AVM syndrome, ~30% of probands have a *de novo* pathogenic variant [Revencu et al 2008]; in *EPHB4*-CM-AVM syndrome, ~20% of affected individuals have a *de novo* pathogenic variant [Vivanti et al 2018, Wooderchak-Donahue et al 2019]; therefore, testing of parental samples for variants identified in a proband may be helpful for the interpretation of the variant. (2) Somatic mosaicism for a *de novo EPHB4* pathogenic variant (identified in ~20% of blood cells) has been reported [Wooderchak-Donahue et al 2019]; therefore, detection of mosaicism should be considered in assay selection and development.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by capillary malformations and/or arteriovenous malformations, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Capillary Malformation-Arteriovenous Malformation (CM-AVM) Syndrome

Gene [1, 2]	Proportion of CM-AVM Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
EPHB4	~10% [6]	54/54 [6]	Unknown [6]
RASA1	~50% [7]	~92% [7, 8]	~8% [7, 8]
Unknown [8]	~40% [6]	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Amyere et al [2017] reported 54 index patients identified by sequence analysis.
7. Revencu et al [2008], Revencu et al [2013b]
8. Wooderchak-Donahue et al [2018]

Clinical Characteristics

Clinical Description

The clinical manifestations of *RASA1*-capillary malformation-arteriovenous malformation (*RASA1*-CM-AVM) syndrome have been described in many individuals with large cohorts by Eerola et al [2003] (n=39), Revencu et al [2008] (n=101), and Revencu et al [2013b] (n=138), with insights from a number of other case series and case reports [Hershkovitz et al 2008a, Hershkovitz et al 2008b, Thiex et al 2010, Carr et al 2011, Buhl et al 2012, de Wijn et al 2012, Wooderchak-Donahue et al 2012, Burrows et al 2013, Català et al 2013, Durrington et al 2013, Kim et al 2015, Maruani et al 2018, Wooderchak-Donahue et al 2018].

The clinical manifestations of *EPHB4* capillary malformation-arteriovenous malformation (*EPHB4*-CM-AVM) syndrome have been described in two studies by Amyere et al [2017] (n=102), and Wooderchak-Donahue et al [2019] (n=10).

Significant intra- and interfamilial variability in the existence and location of vascular malformations has been described.

Table 2. Features of Capillary Malformation-Arteriovenous Malformation

Feature	% of Persons with Feature by Associated Gene	
	RASA1-CM-AVM [1]	*EPHB4*-CM-AVM [2]
Capillary malformations	~97%	100%
Arteriovenous malformations/ arteriovenous fistulas [3]	~24% includes: • 13% extra-CNS • 10% intra-CNS	~18% includes: • Mostly AVM & extracranial • 1% vein of Galen aneurysmal malformation
Parkes Weber syndrome	8%	8%
Bier spots	None reported	12%

Table 2. continued from previous page.

Feature	% of Persons with Feature by Associated Gene	
	RASA1-CM-AVM [1]	*EPHB4*-CM-AVM [2]
Telangiectasias (upper thorax, lips, or arms/legs)	None reported	~80% [2]
Epistaxis	None reported	~60% [2]

1. Revencu et al [2013b]
2. An ascertainment bias exists for the two studies included. In the first large study individuals were ascertained for CM-AVM syndrome [Amyere et al 2017], and in the second small study for hereditary hemorrhagic telangiectasia [Wooderchak-Donahue et al 2019]. In this second group, epistaxis and telangiectasia ratio was higher than in the first study (epistaxis: 6/10 individuals; telangiectasia: 8/10 individuals; CM: 8/10 individuals).
3. Not all individuals with CM-AVM syndrome are likely to have had comprehensive imaging studies; therefore, the frequency of AVMs/AVFs is difficult to determine.

Capillary Malformations (CMs)

CMs are multiple round or oval pink lesions often with a blanched halo. CMs can be present at birth and tend to increase in number over time.

Arterial flow with Doppler ultrasound has been reported over the CMs [Kim et al 2015] and is hypothesized to be a manifestation of an underlying AVM. It is unclear if arterial flow abnormalities associated with the CMs can increase or develop over time.

Arteriovenous Malformations / Arteriovenous Fistulas (AVMs/AVFs)

Current data on long-term development of AVMs/AVFs after initial screening are insufficient. Although it has been hypothesized that AVMs/AVFs may develop over time [Orme et al 2013], to date no individuals who had normal imaging screens have subsequently been reported to have developed AVMs/AVFs.

Intracranial AVMs/AVFs can manifest early in life [Revencu et al 2008, Revencu et al 2013b]. Vein of Galen aneurysmal malformation and other intracranial AVMs have led to seizures, hydrocephalus, migraine headaches, and cardiac failure [Eerola et al 2003, Revencu et al 2008, Grillner et al 2016, Amyere et al 2017]. Vivanti et al [2018] reported on a series of 19 children with vein of Galen malformation; 10% had *EPHB4* pathogenic variants.

Revencu et al [2008] reported that most of the intracranial lesions were macrofistulas causing symptoms in infancy. However, this finding may be biased given that the identification of the AVMs/AVFs may be secondary to associated symptoms and that asymptomatic individuals may not have had the imaging studies needed to detect the lesions.

Extracranial AVMs and AVFs are typically reported in skin, muscle, and spine.

Although approximately 50% of AVMs/AVFs have been reported to be in the head/neck region [Revencu et al 2013b], the frequency of AVMs/AVFs in this location may be an overestimate because it is likely that imaging is preferentially performed in this region.

Symptomatic intraspinal AVMs resulting in neurologic deficits have been reported; MRI has identified intraspinous lesions requiring endovascular/surgical treatment [Thiex et al 2010].

AVMs/AVFs have not been commonly reported in viscera [Revencu et al 2008], a distinguishing difference from hereditary hemorrhagic telangiectasia.

Parkes Weber Syndrome

Limb overgrowth has been reported in both the upper and lower extremities in individuals with CM-AVM syndrome. The overgrowth is typically noticeable in infancy and can range in severity. Most individuals with limb overgrowth fulfill the findings of Parkes Weber syndrome, defined by Revencu et al [2013b] as the presence of a capillary stain, bony and soft tissue hyperplasia, and multiple arteriolovenular microfistulas throughout an upper or lower extremity [Amyere et al 2017].

Other

Bier spots, white spots on the skin surrounded by a pale halo of erythema, have been described in individuals with *EPHB4*-CM-AVM syndrome [Amyere et al 2017, Wooderchak-Donahue et al 2019].

Telangiectasia has been reported primarily in individuals with *EPHB4*-CM-AVM syndrome. The telangiectases were typically located on the lips, trunks, and/or arms/legs [Amyere et al 2017, Wooderchak-Donahue et al 2019].

Epistaxis has been reported in individuals with *EPHB4*-CM-AVM syndrome [Amyere et al 2017, Wooderchak-Donahue et al 2019].

Cardiac overload/failure is a potential complication in individuals with significant fast-flow lesions.

In particular, one third of individuals with *RASA1* Parkes Weber syndrome required cardiac follow up [Revencu et al 2008].

One infant with *RASA1*-CM-AVM syndrome had an AVF between the left carotid artery and jugular vein that caused cardiac overload requiring treatment [Eerola et al 2003].

One woman with *RASA1*-CM-AVM syndrome reported worsening of symptoms during pregnancy; she developed pulmonary and peripheral edema with concern for high-output heart failure that resolved after pregnancy [Durrington et al 2013].

Nonimmune hydrops fetalis due to an AVM has been reported in *RASA1*-CM-AVM syndrome [Overcash et al 2015].

Congenital heart defects have been reported in a few individuals with *RASA1*- and *EPHB4*-CM-AVM syndrome; however, this finding may be coincidental [Revencu et al 2008, Martin-Almedina et al 2016].

Lymphatic malformations have been reported in several individuals with *EPHB4*- and *RASA1*-CM-AVM syndrome [de Wijn et al 2012, Burrows et al 2013, Macmurdo et al 2016]. Lymphangiography and near-infrared fluorescence lymphatic imaging showed abnormally dilated collecting lymphatics with sluggish flow in the unaffected limb, and tortuous lymphatics of the affected limb with lymphocele-like vesicles in the groin of individuals with *RASA1*-CM-AVM syndrome [Burrows et al 2013]. Whether these lymphatic abnormalities are progressive is not yet known. An *EPHB4* pathogenic variant was identified in a four-generation pedigree with central conducting lymphatic anomaly [Li et al 2018]. Hydrops fetalis was reported in individuals from two families with *EPHB4*-CM-AVM syndrome [Martin-Almedina et al 2016].

Tumors. Individuals with *RASA1*-CM-AVM syndrome may be at increased risk for tumor development, but review of the reported cases does not confirm this: Revencu et al [2008] reported several different types of tumors (e.g., optic glioma, lipoma, superficial basal cell carcinoma, angiolipoma, non-small-cell lung cancer, and vestibular schwannoma) in 44 families; however, in their larger series of 138 individuals, the only tumors reported were two common basal cell carcinomas in two individuals from the same family [Revencu et al 2013b]. Whether the rate of tumors is increased compared to the general population is as yet unknown, but it is likely not dramatically increased.

Additional findings observed in a small number of individuals with *RASA1*-CM-AVM syndrome include seizures, headaches, hydrocephalus, neurogenic bladder, varicosities, and hemangiomas. It is not clear if these findings are primary manifestations of a germline heterozygous *RASA1* pathogenic variant, secondary complications of AVMs/AVFs, or unrelated.

Genotype-Phenotype Correlations

Studies to date are insufficient to identify genotype-phenotype correlations.

Penetrance

EPHB4. Penetrance of *EPHB4*-CM-AVM syndrome was reported to be 93% (102 of 110 individuals) in one study by Amyere et al [2017].

RASA1. Penetrance is 90%-99% for *RASA1*-CM-AVM syndrome. Revencu et al [2008] determined that 55 of 57 individuals heterozygous for a germline *RASA1* pathogenic variant were affected. Revencu et al [2013b] determined that 136 of 138 individuals heterozygous for a germline *RASA1* pathogenic variant had multiple CMs.

Nomenclature

Eerola et al [2003] named the phenotype caused by *RASA1* pathogenic variants "capillary malformation-arteriovenous malformation" (CM-AVM) syndrome. Later, Amyere et al [2017] named the phenotype caused by *RASA1* pathogenic variants "capillary malformation-arteriovenous malformation 1" (CM-AVM1) and the phenotype caused by *EPHB4* pathogenic variants "capillary malformation-arteriovenous malformation 2" (CM-AVM2).

Prevalence

Prevalence of CM-AVM syndrome is estimated at 1:100,000 in northern Europeans [Revencu et al 2008]. Another estimate of prevalence using the Exome Aggregation Consortium dataset is around 1:20,000 (*RASA1*-CM-AVM syndrome) and 1:12,000 (*EPHB4*-CM-AVM syndrome) [Amyere et al 2017].

Genetically Related (Allelic) Disorders

RASA1. No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *RASA1*.

Developmental delay and severe neurologic findings were reported in individuals with deletions encompassing *RASA1* and *MEF2C* [Carr et al 2011], but it is thought that these findings are not secondary to deletion of *RASA1*. (See Differential Diagnosis.)

EPHB4. No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *EPHB4*.

Differential Diagnosis

Table 3. Other Genes of Interest in the Differential Diagnosis of Capillary Malformation-Arteriovenous Malformation (CV-AVM) Syndrome

Gene(s)	Differential Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/CV-AVM syndrome	Distinguishing from CV-AVM syndrome
ACVRL [1] *ENG* [1] *GDF2* [1] *SMAD4* [1]	Hereditary hemorrhagic telangiectasia	AD	Multiple AVMs that lack intervening capillaries & result in direct connections between arteries & veins	• Spontaneous & recurrent nosebleeds (epistaxis) are more common. • Telangiectases generally only on lips, nose, & hands • ~25% may have GI bleeding later in life. • Large capillary malformations are not typical.
GNAQ	Sturge-Weber syndrome (SWS) (OMIM 185300)	See footnote 2.	Intracranial vascular anomaly [3]	Segmental facial cutaneous vascular malformations (port-wine stains), seizures, & glaucoma [4]
PIK3CA	Klippel-Trenaunay-Weber syndrome [5]	See footnote 6.	CMs & hypertrophy of the related bones & soft tissues	Vascular malformations are typically low-flow lesions w/o high-flow AVMs. [7]
PTEN	*PTEN* hamartoma tumor syndromes [8]	AD	Overgrowth & fast-flow lesions	• Vascular anomalies are usually intramuscular, assoc w/ectopic fat, & severely disrupt tissue architecture. [9] • Tumor predisposition is more prominent.
TEK	Multiple cutaneous and mucosal venous malformations	AD	Cutaneous VMs can be mistaken for CMs.	• Small, multifocal bluish cutaneous &/or mucosal VMs, usually present at birth. New lesions appear w/time. • Small lesions are usually asymptomatic; larger lesions can invade subcutaneous muscle & cause pain.

Table 3. continued from previous page.

Gene(s)	Differential Disorder	MOI	Clinical Features of Differential Disorder	
			Overlapping w/CV-AVM syndrome	Distinguishing from CV-AVM syndrome
GLMN	Hereditary glomuvenous malformations (GVMs) (OMIM 138000)	AD	Cutaneous VMs can be mistaken for CMs.	• Clinically GVM can look like any VM, but GVMs are more painful on palpation, only partially compressible, & usually not found in mucosa. [10] • Lesions consist of glomus cells. • Familial aggregation is generally more common in hereditary GVM than in VMs.

AD = autosomal dominant; AVM = arteriovenous malformation; CM = capillary malformation; MOI = mode of inheritance; VM = venous malformation

1. The known hereditary hemorrhagic telangiectasia-related genes are involved in the TGF-β/BMP signaling cascade.

2. Somatic mosaic mutation of *GNAQ* has been reported in individuals with Sturge-Weber syndrome [Shirley et al 2013].

3. Leptomeningeal angiomatosis most often involves the occipital and posterior parietal lobes.

4. No *RASA1* pathogenic variants were identified in nine persons with SWS who represented simplex cases (i.e., a single occurrence in a family) [Zhou et al 2011] or in 37 individuals with SWS [Revencu et al 2013b].

5. Also referred to as Klippel-Trenaunay syndrome (KTS)

6. Mosaic variants in *PIK3CA* have been reported in KTS [Vahidnezhad et al 2016].

7. Diagnostic criteria for KTS have been proposed [Oduber et al 2008]. To date no *RASA1* pathogenic variants have been identified in individuals with typical Klippel-Trenaunay syndrome [Revencu et al 2013a].

8. *PTEN* hamartoma tumor syndromes include Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-Proteus syndrome, and Proteus-like syndrome.

9. Caux et al [2007], Tan et al [2007]

10. Hereditary GVMs have a cobblestone appearance with a consistency harder than that of venous malformations. Histologically, glomuvenous malformations are distinguishable by the presence of pathognomonic rounded cells (glomus cells) around the distended vein-like channels [Brouillard et al 2002].

Hereditary benign telangiectasia (OMIM 187260). Some of the cutaneous AVMs in the autosomal dominant disorder hereditary benign telangiectasia (HBT) can be of similar size to those seen in CM-AVM syndrome. However, solid organ AVMs are not seen in HBT.

Deletion 5q14.3q15. Individuals with microdeletion of 5q14.3q15 including *RASA1* and neighboring genes have been reported [Carr et al 2011, Zweier & Rauch 2012]. Findings included multifocal CMs and severe developmental delay associated with *MEF2C* haploinsufficiency. In their review of the findings in four other individuals previously reported with deletions of both *RASA1* and *MEF2C*, Carr et al [2011] determined that CMs had not been reported, but the report by Zweier and Rauch [2012] showed images of a child with multiple round capillary malformations of variable sizes. The severe developmental delays are not thought to result from deletion of *RASA1*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with capillary malformation-arteriovenous malformation (CM-AVM) syndrome, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Medical history and physical examination with a focus on symptoms and findings secondary to arteriovenous malformations/arteriovenous fistulas (AVMs/AVFs)

- Brain imaging – if not already performed – to identify AVMs/AVFs (e.g., vein of Galen aneurysms and other intracranial AVMs) to allow early identification of macrofistulas that can be treated prior to the development of symptoms [Revencu et al 2008]
- Consideration of spine imaging to identify and characterize AVMs/AVFs. Currently no consensus protocols for radiographic evaluation of individuals with CM-AVM syndrome have been developed; therefore, discussion with a radiologist is recommended in order to develop an appropriate plan for imaging based on the patient's age and the capabilities and experience of the imaging facility.
- Consideration of further imaging in individuals with evidence of cardiac overload, to look for causative AVMs/AVFs
- Evaluation for evidence of epistaxis (nosebleeds), and if present, referral to otolaryngologist as appropriate. If epistaxis is present, consider complete blood count for evaluation of anemia.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with CM-AVM Syndrome

Manifestation/Concern	Treatment	Considerations/Other
CMs & telangiectases	Referral to dermatologist	To evaluate CMs of cosmetic concern & discuss risks & benefits of intervention
AVMs/AVFs	Multidisciplinary team incl specialists in interventional radiology, neurosurgery, surgery, cardiology, & dermatology depending on location & symptoms	• To determine treatment (e.g., embolization vs surgery) • Risks & benefits of intervention for AVMs & AVFs must be considered.
Cardiac overload	Referral to cardiologist	
Hemihyperplasia &/or leg length discrepancy	Referral to orthopedist	Consider: • Lymphangiography to evaluate for lymphatic malformations; • Compression stockings for those w/evidence of lymphedema.
Epistaxis (nosebleeds)	Humidification & nasal lubricants; referral to otolaryngologist	If epistaxis, perform complete blood count for eval of anemia.

Surveillance

The clinician should have a low threshold to repeat imaging studies if clinical signs/symptoms of AVMs/AVFs become evident over time.

Agents/Circumstances to Avoid

Although no agents/circumstances resulting in complications of CM-AVM syndrome have been reported, a theoretic consideration is avoidance of routine use of anticoagulants unless indicated for treatment of a different medical condition.

Evaluation of Relatives at Risk

Clarification of the genetic status of at-risk relatives is appropriate in order to allow early diagnosis and treatment of AVMs/AVFs to reduce/avoid secondary adverse outcomes. In particular, at-risk infants are candidates for prompt diagnosis given the possible early presentation of neurologic complications from intracranial AVMs/AVFs [Revencu et al 2008].

Evaluations can include:

- Molecular genetic testing if the *RASA1* or *EPHB4* pathogenic variant in the family is known;
- Physical evaluation of the skin to look for capillary malformations if the pathogenic variant in the family is not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 70% of individuals diagnosed with *RASA1*-CM-AVM syndrome have an affected parent; about 80% of individuals diagnosed with *EPHB4*-CM-AVM syndrome have an affected parent.
- A proband with CM-AVM syndrome may have the disorder as the result of a *de novo RASA1* or *EPHB4* pathogenic variant. In *RASA1*-CM-AVM syndrome, approximately 30% of probands have a *de novo* pathogenic variant [Revencu et al 2008]; in *EPHB4*-CM-AVM syndrome, approximately 20% of affected individuals have a *de novo* pathogenic variant [Vivanti et al 2018, Wooderchak-Donahue et al 2019]. Note: Somatic mosaicism for a *de novo EPHB4* pathogenic variant (identified in ~20% of blood cells) was reported in one affected proband [Wooderchak-Donahue et al 2019].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Although no instances of parental germline mosaicism have been reported, it remains a possibility.
- The family history of an individual diagnosed with CV-AVM syndrome may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *RASA1* or *EPHB4* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, the sibs of a proband with clinically unaffected parents are still at increased risk for CV-AVM syndrome because of the possibility of reduced penetrance in a parent.

Offspring of a proband. Each child of an individual with a CV-AVM syndrome has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *RASA1* or *EPHB4* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the CV-AVM syndrome causative pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

No specific resources for Capillary Malformation-Arteriovenous Malformation Syndrome have been identified by *GeneReviews* staff.

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Capillary Malformation-Arteriovenous Malformation Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EPHB4	7q22.1	Ephrin type-B receptor 4		EPHB4	EPHB4
RASA1	5q14.3	Ras GTPase-activating protein 1	ARUP RASA1 Database RASA1base: Database for pathogenic mutations in the RasGAP SH2 domain Vascular Anomaly and Lymphedema Mutation Database - RASA1	RASA1	RASA1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Capillary Malformation-Arteriovenous Malformation Syndrome (View All in OMIM)

139150	RAS p21 PROTEIN ACTIVATOR 1; RASA1
600011	EPHRIN RECEPTOR EphB4; EPHB4
608354	CAPILLARY MALFORMATION-ARTERIOVENOUS MALFORMATION 1; CMAVM1
618196	CAPILLARY MALFORMATION-ARTERIOVENOUS MALFORMATION 2; CMAVM2

Molecular Pathogenesis

The protein RASA1 switches the active GTP-bound Ras to the inactive GDP-bound form. It is a negative regulator of the Ras/MAPK-signaling pathway, which mediates cellular growth, differentiation, and proliferation from various protein kinases on cell surfaces.

Germline heterozygous *RASA1* pathogenic variants result in constitutive activation of Ras and resistance to GTPase-activating proteins GAPs.

EPHB4 and its ligand, EphrinB2, are transmembrane proteins, receptor and ligand, respectively. These two proteins act in concert with Notch signaling to control arterial-venous differentiation. EphrinB2-EPHB4 interactions suppress RAS-MAPK-ERK1/2 and P13K-AKT-MTORC1 pathways [Xiao et al 2012, Amyere et al 2017]. EPHB4 is expressed in venous endothelial cells during vascular development [Adams et al 1999] and lack of the protein may lead to disorganized vascular development.

Mechanism of disease causation. Based on the currently identified pathogenic variants in *RASA1*, haploinsufficiency is a suggested mechanism for the disease. Second hits have been proposed as a mechanism for development of the vascular lesions [Revencu et al 2013b, Macmurdo et al 2016, Lapinski et al 2018].

Loss of function of *EPHB4* is a suggested mechanism. *EPHB4* pathogenic variants reported include nonsense, frameshift, and splice site variants [Amyere et al 2017, Wooderchak-Donahue et al 2019].

Chapter Notes

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- 12 September 2019 (sw) Comprehensive update posted live
- 6 October 2016 (bp) Comprehensive update posted live
- 19 December 2013 (me) Comprehensive update posted live
- 22 February 2011 (me) Review posted live
- 6 December 2010 (pbt) Original submission

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