ISSVA classification for vascular anomalies ©

(Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018)

This classification is intended to evolve as our understanding of the biology and genetics of vascular malformations and tumors continues to grow

Overview table

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined °**	**of major named vessels**	**associated with other anomalies**
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

° defined as two or more vascular malformations found in one lesion
* high-flow lesions

A list of causal genes and related vascular anomalies is available in Appendix 2

The tumor or malformation nature or precise classification of some lesions is still unclear. These lesions appear in a separate provisional list.

Abbreviations used

For more details, click on the underlined links

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ISSVA classification of vascular tumors 1a

Type Alt ← for previous view

Benign vascular tumors 1	
Infantile hemangioma / Hemangioma of infancy	see details
Congenital hemangioma Rapidly involuting (RICH) * Non-involuting (NICH) Partially involuting (PICH)	GNAQ / GNA11
Tufted angioma * °	GNA14
Spindle-cell hemangioma	IDH1 / IDH2
Epithelioid hemangioma	FOS
Pyogenic granuloma (also known as lobular capillary hemangioma)	BRAF / RAS / GNA14
Others	see details

* some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

° many experts believe that tufted angioma and kaposiform hemangioendothelioma are part of a spectrum rather than distinct entities

N.B. reactive proliferative vascular lesions are listed with benign tumors

Causal genes in blue

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ISSVA classification of vascular tumors 1b

Type Alt ← for previous view

Benign vascular tumors 2
Others
Hobnail hemangioma
Microvenular hemangioma
Anastomosing hemangioma
Glomeruloid hemangioma
Papillary hemangioma
Intravascular papillary endothelial hyperplasia
Cutaneous epithelioid angiomatous nodule
Acquired elastotic hemangioma
Littoral cell hemangioma of the spleen
Related lesions
Eccrine angiomatous hamartoma
Reactive angioendotheliomatosis
Bacillary angiomatosis

N.B. The tumor nature of some of these lesions is not certain

Reactive proliferative vascular lesions are listed with benign tumors

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ISSVA classification of vascular tumors 2

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Locally aggressive or borderline vascular tumors	
Kaposiform hemangioendothelioma * °	GNA14
Retiform hemangioendothelioma	
Papillary intralymphatic angioendothelioma (PILA), Dabska tumor	
Composite hemangioendothelioma	
Pseudomyogenic hemangioendothelioma	FOSB
Polymorphous hemangioendothelioma	
Hemangioendothelioma not otherwise specified	
Kaposi sarcoma	
Others	
Malignant vascular tumors	
Angiosarcoma	(Post radiation) MYC
Epithelioid hemangioendothelioma	CAMTA1 / TFE3
Others	

* some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

° many experts believe that tufted angioma and kaposiform hemangioendothelioma are part of a spectrum rather than distinct entities

N.B. reactive proliferative vascular lesions are listed with benign tumors

Causal genes in blue

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Simple vascular malformations I

Capillary malformations (CM)	
Nevus simplex / salmon patch, “angel kiss”, “stork bite”	
Cutaneous and/or mucosal CM (also known as “port-wine” stain)	
Nonsyndromic CM	GNAQ
CM with CNS and/or ocular anomalies (Sturge-Weber syndrome)	GNAQ
CM with bone and/or soft tissues overgrowth	GNA11
Diffuse CM with overgrowth (DCMO)	GNA11
Reticulate CM	
CM of MIC-CAP (microcephaly-capillary malformation)	STAMBP
CM of MCAP (megalencephaly-capillary malformation-polymicrogyria)	PIK3CA
CM of CM-AVM	RASA1 / EPHB4
Cutis marmorata telangiectatica congenita (CMTC)	
Others	
Telangiectasia*	
Hereditary hemorrhagic telangiectasia (HHT) (*HHT1* ENG, *HHT2* ACVRL1, *HHT3*, *JPHT* SMAD4)	
Others	

* The CM nature of some subtypes of telangiectasia is debated.
Some telangiectasia may be reclassified in other sections in the future

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Simple vascular malformations IIa

Lymphatic malformations (LM)	
Common (cystic) LM *	PIK3CA
Macrocystic LM	
Microcystic LM	
Mixed cystic LM	
Generalized lymphatic anomaly (GLA)	
Kaposiform lymphangiomatosis (KLA)	
LM in Gorham-Stout disease	
Channel type LM	
“Acquired” progressive lymphatic anomaly (so called acquired progressive "lymphangioma")	
Primary lymphedema (different types)	
Others	

* When associated with overgrowth, some of these lesions belong to the PIK3CA-related overgrowth spectrum see details
Some of these lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

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Simple vascular malformations IIb	
Primary lymphedema	
Nonne-Milroy syndrome	FLT4 / VEGFR3
Primary hereditary lymphedema	VEGFC
Primary hereditary lymphedema	GJC2 / Connexin 47
Lymphedema-distichiasis	FOXC2
Hypotrichosis-lymphedema-telangiectasia	SOX18
Primary lymphedema with myelodysplasia	GATA2
Primary generalized lymphatic anomaly (Hennekam lymphangiectasia-lymphedema syndrome)	CCBE1
Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome	KIF11
Lymphedema-choanal atresia	PTPN14

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Simple vascular malformations III	
Venous malformations (VM)	
Common VM	TEK (TIE2) / PIK3CA
Familial VM cutaneo-mucosal (VMCM)	TEK (TIE2)
Blue rubber bleb nevus (Bean) syndrome VM	TEK (TIE2)
Glomuvenous malformation (GVM)	Glomulin
Cerebral cavernous malformation (CCM)	(*CCM1* KRIT1, *CCM2* Malcavernin, *CCM3* PDCD10)
Familial intraosseous vascular malformation (VMOS)	ELMO2
Verrucous venous malformation *(formerly verrucous hemangioma)*	MAP3K3
Others	

some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

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Simple vascular malformations IV	
Arteriovenous malformations (AVM)	
Sporadic	MAP2K1
In HHT	(*HHT1* ENG, *HHT2* ACVRL1, *HHT3*, *JPHT* SMAD4)
In CM-AVM	RASA1 / EPHB4
Others	
Arteriovenous fistula (AVF) (congenital)	
Sporadic	MAP2K1
In HHT	(*HHT1* ENG, *HHT2* ACVRL1, *HHT3*, *JPHT* SMAD4)
In CM-AVM	RASA1 / EPHB4
Others	

Abbreviations used

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ISSVA classification for vascular anomalies

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Combined vascular malformations*		
CM + VM	capillary-venous malformation	CVM
CM + LM	capillary-lymphatic malformation	CLM
CM + AVM	capillary-arteriovenous malformation	CAVM
LM + VM	lymphatic-venous malformation	LVM
CM + LM + VM	capillary-lymphatic-venous malformation	CLVM
CM + LM + AVM	capillary-lymphatic-arteriovenous malformation	CLAVM
CM + VM + AVM	capillary-venous-arteriovenous malformation	CVAVM
CM + LM + VM + AVM	capillary-lymphatic-venous-arteriovenous m.	CLVAVM

* defined as two or more vascular malformations found in one lesion

Abbreviations used

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Anomalies of major named vessels

(also known as "channel type" or "truncal" vascular malformations)

Affect
- lymphatics
- veins
- arteries

Anomalies of
- origin
- course
- number
- length
- diameter (aplasia, hypoplasia, stenosis, ectasia / aneurysm)
- valves
- communication (AVF)
- persistence (of embryonal vessel)

Abbreviations used

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ISSVA classification for vascular anomalies

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Vascular malformations associated with other anomalies		
Klippel-Trenaunay syndrome: *	CM + VM +/- LM + limb overgrowth	PIK3CA
Parkes Weber syndrome:	CM + AVF + limb overgrowth	RASA1
Servelle-Martorell syndrome:	limb VM + bone undergrowth	
Sturge-Weber syndrome:	facial + leptomeningeal CM + eye anomalies +/- bone and/or soft tissue overgrowth	GNAQ
Limb CM + congenital non-progressive limb overgrowth		GNA11
Maffucci syndrome:	VM +/- spindle-cell hemangioma + enchondroma	IDH1 / IDH2
Macrocephaly - CM (M-CM / MCAP) *		PIK3CA
Microcephaly - CM (MICCAP)		STAMBP
CLOVES syndrome: *	LM + VM + CM +/- AVM + lipomatous overgrowth	PICK3CA
Proteus syndrome:	CM, VM and/or LM + asymmetrical somatic overgrowth	AKT1
Bannayan-Riley-Ruvalcaba sd:	AVM + VM +macrocephaly, lipomatous overgrowth	PTEN
CLAPO syndrome: *	lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth	PIK3CA

Abbreviations used

* these lesions belong to the PIK3CA-related overgrowth spectrum (PROS) see details

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Provisionally unclassified vascular anomalies	
Intramuscular hemangioma *	
Angiokeratoma	
Sinusoidal hemangioma	
Acral arteriovenous "tumour"	
Multifocal lymphangioendotheliomatosis with thrombocytopenia / cutaneovisceral angiomatosis with thrombocytopenia (MLT/CAT)	
PTEN (type) hamartoma of soft tissue / "angiomatosis" of soft tissue (PHOST)	PTEN
Fibro adipose vascular anomaly (FAVA)	PIK3CA

* Distinct from infantile hemangioma, from intramuscular common VM, PHOST/AST, FAVA and AVM some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

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Appendix 1
abbreviations used (excluding gene names)

Type Alt ← for previous view

AST	angiomatosis of soft tissue
AVF	arteriovenous fistula
AVM	arteriovenous malformation
CAT	cutaneovisceral angiomatosis with thrombocytopenia
CAVM	capillary arteriovenous malformation
CCM	cerebral cavernous malformation
CLAVM	capillary lymphatic arteriovenous malformation
CLAPO	lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth
CLOVES	congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal/scoliosis and spinal abnormalities
CLM	capillary lymphatic malformation
CLVAVM	capillary lymphatic venous arteriovenous malformation
CLVM	capillary lymphatic venous malformation
CM	capillary malformation
CM-AVM	capillary malformation-arteriovenous malformation
CMTC	cutis marmorata telangiectatica congenita
CNS	central nervous system
CVAVM	capillary venous arteriovenous malformation
CVM	capillary venous malformation
DCMO	diffuse capillary malformation with overgrowt
DIC	disseminated intravascular coagulopathy
FAVA	Fibro adipose vascular anomaly
GLA	generalized lymphatic anomaly
GSD	Gorham-Stout disease
GVM	glomuvenous malformation

HHT	hereditary hemorrhagic telangiectasia
HI	hemangioma of infancy / infantile hemangioma
IH	infantile hemangioma / hemangioma of infancy
INR	international normalized ratio
JPHT	juvenile polyposis hemorrhagic telangiectasia
KHE	kaposiform hemangioendothelioma
KLA	kaposiform lymphangiomatosis
KMP	Kasabach-Merritt phenomenon,
LM	lymphatic malformation
LVM	lymphatic venous malformation
MCAP	megalencephaly-capillary malformation-polymicrogyria
M-CM	macrocephaly-capillary malformation
MICCAP	microcephaly-capillary malformation
MLT	Multifocal lymphangioendotheliomatosis with thrombocytopenia
NICH	non-involuting congenital hemangioma
PHACE	posterior fossa malformations, hemangioma, arterial anomalies, cardiovascular anomalies, eye anomalies
PHOST	PTEN hamartoma of soft tissue
PILA	papillary intralymphatic angioendothelioma
PICH	partially involuting congenital hemangioma
PROS	PIK3CA-related overgrowth spectrum
RICH	rapidly involuting congenital hemangioma
TA	tufted angioma
VM	venous malformation
VMCM	venous malformation cutaneo mucosal

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Appendix 2a
causal genes of vascular anomalies

ACVRL1	Telangiectasia, AVM and AVF of HHT2
AKT1	Proteus syndrome
BRAF	Pyogenic granuloma PG
CAMTA1	Epithelioid hemangioendothelioma EHE
CCBE1	Primary generalized lymphatic anomaly (Hennekam lymphangiectasia-lymphedema syndrome)
ELMO2	Familial intraosseous vascular malformation VMOS
ENG	Telangiectasia, AVM and AVF of HHT1
EPHB4	CM-AVM2
FLT4	Nonne-Milroy syndrome (gene also named VEGFR3)
FOS	Epithelioid hemangioma EH
FOSB	Pseudomyogenic hemangioendothelioma
FOXC2	Lymphedema-distichiasis
GATA2	Primary lymphedema with myelodysplasia
GJC2	Primary hereditary lymphedema
Glomulin	Glomuvenous malformation
GNA11	Congenital hemangioma CH CM with bone and/or soft tissue hyperplasia Diffuse CM with overgrowth DCMO
GNA14	Tufted angioma TA Pyogenic granuloma PG Kaposiform hemangioendothelioma KHE
GNAQ	Congenital hemangioma CH CM "Port-wine" stain, nonsyndromic CM CM of Sturge-Weber syndrome

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Appendix 2b
causal genes of vascular anomalies

IDH1	Maffucci syndrome Spindle-cell hemangioma
IDH2	Maffucci syndrome Spindle-cell hemangioma
KIF11	Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome
KRIT1	Cerebral cavernous malformation CCM1
Malcavernin	Cerebral cavernous malformation CCM2
MAP2K1	Arteriovenous malformation AVM (sporadic)
MAP2K1	Ateriovenous fistula AVF (sporadic)
MAP3K3	Verrucous venous malformation (somatic)
MYC	Post radiation angiosarcoma
NPM11	Maffucci syndrome
PDCD10	Cerebral cavernous malformation CCM3
PIK3CA	Common (cystic) LM (somatic)* Common VM (somatic)* Klippel-Trenaunay syndrome* Megalencephaly-capillary malformation-polymicrogyria (MCAP)* CLOVES syndrome* CLAPO syndrome* Fibro adipose vascular anomaly FAVA

* some of these lesions, associated with overgrowth, belong to the PIK3CA related overgrowth spectrum PROS see details

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Appendix 2c
causal genes of vascular anomalies

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PTEN	Bannayan-Riley-Ruvalcaba syndrome PTEN (type) Hamartoma of soft tissue / "angiomatosis" of soft tissue
PTPN14	Lymphedema-choanal atresia
RAS	Pyogenic granuloma PG
RASA1	CM-AVM1 Parkes Weber syndrome
SMAD4	Telangiectasia, AVM and AVF of Juvenile polyposis hemorrhagic telangiectasia JPHT
SOX18	Hypotrichosis-lymphedema-telangiectasia
STAMBP	Microcephaly-CM (MIC-CAP)
TEK (TIE2)	Common VM (somatic) Familial VM cutaneo-mucosal VMCM Blue rubber bleb nevus (Bean) syndrome (somatic)
TFE3	Epithelioid hemangioendothelioma EHE
VEGFC	Primary hereditary lymphedema
VEGFR3	Nonne-Milroy syndrome (gene also named FLT4)

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Appendix 3
infantile hemangioma

Pattern
- focal - multifocal - segmental - indeterminate

Different types
- superficial - deep - mixed (superficial + deep) - reticular / abortive / minimal growth - others

Association with other lesions	
PHACE association / syndrome	Posterior fossa malformations, Hemangioma, Arterial anomalies, Cardiovascular anomalies, Eye anomalies, sternal clefting and/or supraumbilical raphe
LUMBAR (SACRAL, PELVIS) association / syndrome	Lower body hemangioma, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies, and Renal anomalies

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Appendix 4
vascular anomalies
possibly associated with platelet count / coagulation disorders

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Anomalies	Hematological disorders
Tufted angioma Kaposiform hemangioendothelioma	Profound and sustained thrombocytopenia with profound hypofibrinogenemia, consumptive coagulopathy and elevated D-dimer (Kasabach-Merritt phenomenon)
Rapidly involuting congenital hemangioma	Transient mild/moderate thrombocytopenia, +/- consumptive coagulopathy and elevated D-dimer
Venous malformations / Lymphatic-venous malformations	Chronic localized intravascular coagulopathy with elevated D-dimer, +/- hypofibrinogenemia, and +/- moderate thrombocytopenia (may progress to DIC after trauma or operation)
Lymphatic malformations	Chronic localized intravascular coagulopathy with elevated D-dimer and +/- mild to moderate thrombocytopenia *(consider Kaposiform lymphangiomatosis)* (may progress to DIC after trauma or operation)
Multifocal lymphangioendotheliomatosis with thrombocytopenia / Cutaneovisceral angiomatosis with thrombocytopenia	Sustained, fluctuating, moderate to profound thrombocytopenia with gastrointestinal tract bleeding or pulmonary hemorrhage
Kaposiform lymphangiomatosis	Mild/moderate thrombocytopenia, +/-hypofibrinogenemia, and D-dimer elevation

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Appendix 5
PIK3CA-related overgrowth spectrum

PIK3CA-related overgrowth spectrum (PROS) groups lesions with heterogeneous segmental overgrowth phenotypes -with or without vascular anomalies- due to somatic PIK3CA activating mutations.

This spectrum includes:

- Fibroadipose hyperplasia or Overgrowth (FAO)
- Hemihyperplasia Multiple Lipomatosis (HHML)
- Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal (CLOVES) syndrome
- Macrodactyly
- Fibroadipose Infiltrating Lipomatosis / Facial Infiltrative Lipomatosis
- Megalencephaly-Capillary Malformation (MCAP or M-CM)
- Dysplastic Megalencephaly (DMEG)
- Klippel-Trenaunay syndrome