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Genetics of vascular malformations

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ABSTRACT

Vascular anomalies are developmental defects of the vasculature and encompass a variety of disorders. The majority of these occur sporadically, yet a few are reported to be familial. The identification of genes mutated in the different malformations provides insight into their etiopathogenic mechanisms and the specific roles the associated proteins play in vascular development and maintenance. It is becoming evident that somatic mosaicism plays a major role in the formation of vascular lesions. The importance of utilizing Next-Generating Sequencing (NGS) for high-throughput and "deep" screening of both blood and lesional DNA and RNA is thus emphasized, as the somatic changes are present in low quantities. There are several examples where NGS has already accomplished discovering these changes. The identification of all the causative genes and unraveling of a holistic overview of the pathogenic mechanisms should enable generation of in vitro and in vivo models and lead to development of more effective treatments, not only targeted on symptoms.

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Introduction

Vascular anomalies refer to a wide variety of disorders that result from disruptions in the development and maintenance of the vasculature. The majority of vascular anomalies occur sporadically; however, several can be inherited, predisposing patients to developing vascular lesions. Although the familial cases of vascular malformations occur at a much lower rate, they have been a fundamental starting point to provide insight into the molecules and signaling pathways that play major roles in vascular development and maintenance (Table). The inherited malformations seemingly follow a general pattern. The majority of these are transmitted in an autosomal dominant manner, and mutations tend to result in a loss-of-function of the gene. The phenotypic penetrance, age at onset, and severity of lesions vary greatly among patients, even between individuals of the same family. Inherited malformations are typically multifocal, small, and localized. Cutaneous lesions are the most visible, yet visceral and deeper lesions can also occur. The variability in penetrance and localized nature of these malformations seem to be explained largely by Knudson's two-hit hypothesis: the combination of a germline mutation with a post-zygotic change resulting in localized complete loss of the gene within the lesion, as demonstrated by glomuvenous malformations.[1] Identification of the important role that mutations within the tissue have as second-hits in the familial forms urged studies focusing on somatic changes as the "sole" cause of sporadic lesions.[2,3] Next-Generation Sequencing (NGS) has since proven to be a valuable tool to discover these changes, which often have a low frequency in any given tissue.

Arteriovenous malformations

Arteriovenous malformations (AVMs) and arteriovenous fistulas (AVFs) occur when arteries connect directly to veins, bypassing the capillary beds. Consequently, vessels become dilated and the veins become arterialized. AVMs are characterized by a nidus. These fast-flow lesions can be found anywhere in the body, including the skin and visceral organs.

Hereditary hemorrhagic telangiectasia (HHT, OMIM 187300) is an autosomal dominant inherited disorder where patients are predisposed to developing AVFs/AVMs. The incidence of HHT is 1:5000–1:8000, making it one of the most common inherited vascular malformations. Though it is believed that the vascular defects are present congenitally, most symptoms are seen in older

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Table
Genes mutated in vascular anomalies

Vascular anomaly	Locus	Gene	Inheritance	Mutation affect and type	Normal protein function or involvement
Arteriovenous malformations					
Arteriovenous malformation (AVM)	–	–	Sp	Somatic	–
Hereditary hemorrhagic telangiectasia (HHT)					
HHT1	9q34.11	ENG	AD	LOF and germline	TGF-β/BMP co-receptor
HHT2	12q13.13	ALK1	AD	LOF and germline	TGF-β/BMP type I receptor
HHT3	5q31.3–q32	–	AD	–	–
HHT4	7p14	–	AD	–	–
Juvenile polyposis-HHT (JP-HHT)	18q21.2	MADH4/SMAD4	AD	LOF and germline	Common TGF-β signaling co-mediator
HHT-like	10q11.22	GDF2/BMP9	–	LOF and germline	BMP signaling ligand
Capillary malformations					
Capillary malformation (CM) ("port-wine stain")	9q21	GNAQ	Sp	GOF and somatic mosaicism	α-subunit in Gq class of proteins, regulation of GPCR
Capillary malformation–arteriovenous malformation (CM-AVM)	5q14.3	RASA1	AD/sp	LOF and germline + somatic 2nd hit?	RasGTPase-RAS signaling
Parkes Weber syndrome	5q14.3	RASA1	AD/sp	LOF and germline	Same as above
Sturge–Weber syndrome (SWS)	9q21	GNAQ	Sp	GOF and somatic mosaicism	α-subunit in Gq class of proteins, regulation of GPCR
Cerebral cavernous malformation (CCM)					
CCM1	7q21.2	KRIT1	AD/sp	LOF and germline + somatic 2nd hit/ somatic	Suppress RhoA-GTPase signaling
CCM2	7p13	CCM2/Malcavernin	AD/sp	LOF and germline + somatic 2nd hit/ somatic	Suppress RhoA-GTPase signaling
CCM3	3q26.1	PDCD10	AD/sp	LOF and germline + somatic 2nd hit/ somatic	Apoptosis
CCM4	3q26.3–27.2	–	–	–	–
Venous malformations					
Venous malformation (VM)	9p21.2	TEK/TIE2	Sp	GOF and somatic mosaicism	EC-specific tyrosine kinase receptor for angiopoietins
Cutaneomucosal VM (VMCM)	9p21.2	TEK/TIE2	AD	GOF and germline + somatic 2nd hit	Same as above
Blue rubber bleb nevus syndrome (BRBN)	9p21.2	TEK/TIE2	Sp	GOF and somatic mosaicism	Same as above
Glomuvenous malformation (GVM)	1p22.1	Glomulin	AD	LOF and germline + somatic 2nd hit	Intracellular signaling, cell cycle regulation
Lymphatic malformations					
Lymphatic malformation (LM)	–	–	–	–	
Primary lymphedema (LE)					
Primary congenital LE (Nonne–Milroy disease)	5q35.3	FLT4/VEGFR3	AD/AR/Sp	LOF and germline/ somatic	EC-specific tyrosine kinase receptor
Nonne–Milroy-like disease	4q34	VEGFC	AD	LOF and germline	Ligand for VEGFR3
Choanal atresia-LE	1q41	PTPN14	AR	LOF and germline	Protein tyrosine phosphatase
LE–distichiasis–yellow nail syndrome	16q24.1	FOXC2	AD	LOF and germline	Transcription factor
Hypotrichosis–LE–telangiectasia (HLT) syndrome	20q13.33	SOX18	AD/AR/Sp	LOF?/DN and germline	Transcription factor
Hennekam syndrome	18q21.32	CCBE1	AR	LOF	Regulates ADAMTS3-mediated activation of VEGFC
Microcephaly with or without chorioretinopathy, LE, or mental retardation (MCLMR)	10q23.33	KIF11	AD/Sp	LOF and germline/ somatic	Spindle motor protein
X-linked syndrome anhydrotic ectodermal dysplasia with immunodeficiency, osteopetrosis, and LE (OLEDAID)	Xq28	IKBKG/NEMO	X-linked	Hypomorphic	NFκβ transcription regulation
Hereditary LE II (Meige disease)	1q41–42	GJC2/CX47	AD	Missense and germline	Gap junction protein
Oculodentodigital dysplasia-LE	6q22.31	GJA1/CX43	AD	Missense and germline	Gap junction protein
Primary LE-myelodysplasia (Emberger syndrome)	3q21.3	GATA2	AD	LOF and germline	Transcription factor
Combined/complex syndromes					
Congenital, lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies (CLOVES)	3q26.32	PIK3CA	Sp	GOF and somatic mosaicism	110-kD catalytic alpha subunit of PI3K
Klippel–Trenaunay syndrome	5q13.3	AGGF1/VG5Q	Sp/AD?	Somatic/GOF	Pro-angiogenic factor
	3q26.32	PIK3CA		Somatic/GOF	PI3K/AKT signaling
Proteus syndrome	14q32.33	AKT1		Somatic mosaicism/GOF	PI3K/AKT signaling
PTEN hamartoma tumor syndrome (PHTS)	10q23.31	PTEN	AD	LOF	Dual-specificity protein phosphatase for PI3K/AKT signaling

AD, autosomal dominant; AR, autosomal recessive; DN, dominant negative; Sp, sporadic; LOF, loss-of-function; GOF, gain-of-function; EC, endothelial cell; ECM, extracellular matrix.

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