Genetics and Syndromes Associated with Vascular Malformations

Kelly Duffy, PhD

KEYWORDS

• Vascular malformation • Genetic syndromes
• Genetic testing • Vascular anomaly • Overgrowth

Historically, vascular malformations were not thought to be the result of genetic abnormalities because most of those presenting clinically are sporadic. However, research in this field has expanded over the last decade, leading to the identification of genetic defects responsible for several inherited forms of vascular malformations and associated syndromes, which has shed light on the pathogenesis of sporadic lesions. This advancement in the field has not only enhanced diagnostic capabilities but has also improved our understanding of the potential role of complex genetic mechanisms in vascular malformation development.

It is important for pediatricians to recognize genetically determined vascular malformations and their associated syndromes because there are several disease-specific risks, including various forms of cancer, coagulopathies, pulmonary embolism, and cardiac overload. Genetic testing may be extremely useful for clinical management, screening, and treatment decision making but should be performed only with proper education of the patients and their families. The clinical characteristics of vascular malformations are discussed in the article by Marilyn Liang elsewhere in this issue; this article focuses on genetic contributions to vascular malformations, vascular malformations in the context of syndromes, and the tests that are available.

CURRENT KNOWLEDGE

Vascular malformations are localized structural defects of the vasculature, named after the type of vessel affected.[1] Although some forms of vascular malformations are inherited, a majority occurs sporadically. It is postulated that vascular

Dermatology Department, Pediatric Dermatology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA
E-mail address: kduffy@mcw.edu

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Table 1
Mutations identified in vascular anomalies and associated syndromes

Malformation	Mode of Inheritance	Locus	Gene	Mutations	Pathways/Functions
Capillary malformation	Sporadic	—	—	—	—
Capillary malformation-arteriovenous malformation	Autosomal dominant	5q13-22	RASA1	Loss of function	Ras-MAPK pathways; cell growth, proliferation, motility, survival
Cerebral cavernous malformation	Sporadic Autosomal dominant	— 7q11-22 7p13 3q26.1 3q26.3-27.2	— KRIT1 Malcavernin PDCD10 —	— Loss of function, somatic second hits	— Adaptor proteins, integrin β1 pathway, cell adhesion, migration
Venous malformation	Sporadic	9p21	TIE2/TEK	Somatic, gain of function	Tyrosine kinase receptor, EC proliferation, migration, survival; smooth muscle cell recruitment; vascular sprouting and maturation
Glomuvenous malformation	Autosomal dominant	1p21-22	GLMN	Loss of function, somatic second hit	TGFβ, HGF pathways; protein synthesis; smooth muscle cell differentiation
Cutaneomucosal venous malformation	Autosomal dominant	9p21	TIE2/TEK	Gain of function	Tyrosine kinase receptor; smooth muscle cell recruitment, vascular sprouting, EC proliferation and migration
Lymphatic malformation	Sporadic	—	—	—	—
Primary lymphedema (Milroy disease)	Sporadic Autosomal dominant/ recessive	5q35.3	VEGFR3/FLT4	De novo, loss of function Loss of function	Tyrosine kinase receptor; angiogenesis, lymphangiogenesis, EC proliferation, migration, survival