A Review of Vascular Anomalies: Genetics and Common Syndromes

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Abstract

Keywords

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Vascular tumors and malformations are unique in that affected cells exhibit disrupted angiogenesis. The current treatment options often yield suboptimal results. New insight into the genetics and molecular basis of vascular anomalies may pave the way for potential development of targeted therapy. The authors review the genetic and molecular basis of vascular anomalies and common associated syndromes.

Vascular anomalies were once felt to be purely sporadic lesions. Although this is true in the vast majority of cases, development in the field of genetics has provided new insight into their formation. Moreover, continued advancement in the field of genetics may play a key role in the management of patients with vascular anomalies, including novel approaches to diagnosis and opportunities for disease-specific therapies.

In this article, we will focus solely on reviewing the genetic and molecular basis of some of the more common syndromes associated with vascular anomalies. Syndromes are discussed according to the presenting vascular lesion, which is classified as either vascular tumor or vascular malformation following the widely accepted classification system of the International Society for the Study of Vascular Anomalies (ISSVA).^{1,2} Vascular malformations are further subcategorized into capillary, venous, lymphatic, arteriovenous and mixed malformations.

Vascular Tumors (Hemangiomas)

Although extensive discussion about the differences between vascular tumors (hemangiomas) and malformations is beyond the scope of this article, it is worthwhile highlighting key histological and genetic differences for proper discussion. Although hemangiomas have historically been considered vascular malformation, it is important to note that they are

histologically distinct based on cellular composition as well as clinical behavior. Hemangiomas are neoplastic lesions with endothelial hyperplasia whereas vascular malformations are congenital lesions with normal epithelial turnover.^{1,2} This distinction is of particular importance as it leads to diverging diagnosis as well as treatment of these conditions.³ In terms of clinical presentation, hemangiomas are not typically present at birth, but instead appear shortly after and demonstrate rapid postnatal growth followed by slow involution. In contrast, vascular malformations are always present at birth.

Histologically, cells of hemangiomas demonstrate rapid endothelial hyperplasia as compared with the flat endothelium of a vascular malformation. This appears to be significant in that expression of various vascular endothelial growth factor receptors (VEGFR) are affected in hemangiomas, with one study demonstrating that VEGFR1 was markedly reduced whereas VEGFR2 activity was increased.⁴ In another study, VEGFR mutations were found to be a polymorphic, particularly those associated with infantile hemangiomas.⁵

Syndromes associated with hemangiomas include Von Hippel-Lindau and Maffucci syndromes.

Von Hippel-Lindau Syndrome

Von Hippel-Lindau (VHL) syndrome is an autosomal dominant condition that causes a predisposition to both benign and

malignant neoplasms, including retinal, cerebellar, spinal hemangioblastoma, renal cell carcinoma, pheochromocytoma, and pancreatic tumors.⁶ In particular, the clinical hallmark of VHL is considered angiomas of the retina and hemangioblastoma of the cerebellum. Genetically, there have been several mutations of the VHL tumor suppressor gene, found on chromosome 3, which have been associated with the syndrome.⁷ Notably, VHL can be subdivided into two clinical phenotypes, which have also demonstrated specific genetic associations. Type 1, which presents with retinal and central nervous system (CNS) hemangioblastoma, renal cell carcinoma, but not pheochromocytoma, is generally associated with large deletion or truncation mutations of the VHL gene, thus resulting in little or no function of the transcribed protein. In contrast, type 2, which is characterized by the presence of pheochromocytoma, is usually associated with missense mutation of the VHL gene that results in functional but limited protein.^{6,7} Further evidence of a genotype-phenotype association has also been demonstrated by the lower prevalence of renal cell carcinoma in patients with complete VHL gene deletions.^{8,9}

Maffucci Syndrome

Maffucci syndrome is characterized by spindle cell hemangiomas in addition to enchondromatosis. Notably, the enchondromas associated with Maffucci syndrome have been shown to have malignant potential, with one study demonstrating progression to chondrosarcoma in 30% of the patients.¹⁰ The hemangiomas in this syndrome are generally cutaneous and subcutaneous, rarely causing acute bleeding.¹¹ The inheritance of Maffucci syndrome has mostly been reported as sporadic, with several mutations associated with development of enchondromas.¹² In one study, 77% of patients with Maffucci syndrome carried isocitrate dehydrogenase mutations in their tumors, specifically IDH1 (98%) or IDH2 (2%).¹³ These mutations in cartilage tumors were associated with hypermethylation and downregulated expression of several genes. Notably, even tumors positive for these mutations demonstrated “intraneoplastic mosaicism,” a condition in which there exists a mixture of cells that did and did not express the mutant protein.

Capillary Malformations

The majority of capillary malformations are considered sporadic and not linked to any genetic mutations. A subset of patients will have associated arteriovenous malformations (CM-AVM).¹⁴ These are described as multifocal capillary lesions surrounded by a pale halo and most commonly located on the head and neck. CM-AVM has been linked to an autosomal dominant, loss-of-function mutation in the RASA1 gene, located on 5q11-q23 and encodes p120RASGAP.³ Loss-of-function mutations lead to dysregulation in cell growth and proliferation. Notably, some patients with CM-AVM will have Parkes-Weber syndrome.¹⁴

Sturge-Weber Syndrome

Sturge-Weber syndrome is classically characterized by facial cutaneous capillary malformations (port-wine stains) in

association with intracranial vascular anomalies that can cause seizures and mental retardation. There is no clear hereditary pattern in this syndrome, but there is evidence for somatic mosaicism, which occurs in the somatic cells of the body and is the expression of multiple genotypes due to mitotic errors.¹⁵ Although this is a highly variable syndrome, there is some evidence that the syndrome may be caused by a somatic mosaic mutation in the GNAQ gene on chromosome 9q21,¹⁶ which encodes for guanine nucleotide-binding protein G(q) subunit α . Guanine nucleotide-binding proteins are a family of heterotrimeric proteins that couple transmembrane receptors to intracellular pathways and are activated by a GTPase. Interestingly, the single-nucleotide mutation of GNAQ in vascular endothelial cells seems to occur earlier in development than the mutations that occur in nonsyndromic port-wine stains.¹⁶ Although the exact involvement of this protein in phenotypic expression of Sturge-Weber is unknown, one hypothesis suggests involvement in vasculogenesis via endothelin, which is a G-protein coupled receptor.^{17,18}

Venous Malformations

Venous malformations are the most common vascular malformation evaluated in referral centers. Vikkula et al estimate the incidence to range from 1 in 5,000 to 10,000 live births.¹⁹ These slow-flow lesions are classically blue-violet in color, but can vary widely in clinical presentation. It is crucial to properly identify these anomalies as they can be associated with coagulopathies. A small subset of cutaneomucosal venous malformations is inherited in an autosomal dominant manner. Two large families with known inherited venous malformations have demonstrated single amino acid substitution (R849W) in the gene encoding a tyrosine kinase receptor (TIE2) exclusive to endothelial cells.¹⁹ Although the effects of the substitution are not yet known, it is proposed that mutant TIE2 receptors disrupts the cell cycle of endothelium, ultimately leading to an absence of smooth muscle cells within the malformation, a histological feature unique to cutaneomucosal venous malformations.¹⁹

Another subset of venous malformation is the glomuvenous malformation (GVM), which is a blue-violet raised lesion with a distinct cobblestone surface that is very painful. Lesions contain “glomus cells,” which are modified smooth muscle cells that resemble glomus bodies, the arteriovenous complexes involved in temperature regulation.¹⁹ The gene instigated in GVM development is glomulin, which maps to 1p21-p22.³

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus syndrome (BRBNS), also known as bean syndrome, is a syndrome of generalized small venous malformation found mostly on the trunk and upper arms. These malformations are typically bluish, soft, and easily compressible, and histologically are cavernous spaces lined by a single layer of endothelial cells separated by varying amounts of collagenous and fibrous tissues.^{20,21} Although its lesions have often mistakenly been termed as “angiomas” or

"hemangiomas," it is important to note that they are histologically venous malformations. Genetically, most cases of BRBNS are sporadic, although some familial cases have been linked to chromosome 9p, which encodes for the receptor tyrosine kinase TIE2, believed to be involved in vascular morphogenesis.²² In addition to the skin manifestation of BRBNS, there is also occasional involvement of the gastrointestinal system.²³ Unlike the cutaneous lesions of BRBNS, intestinal lesions can bleed resulting in anemia as well as cause systemic complications such as disseminated intravascular coagulation.²⁴ A few cases of CNS involvement have also been described, in which patients present with focal seizures or other neurologic symptoms as a result of compression from the lesions.²⁵ The lesions of BRBNS usually present at birth or in early childhood and tend to increase in size and frequency with age.²³

Arteriovenous Malformations

Cutaneous arteriovenous malformations (AVMs) are not believed to be heritable with the exception of hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant disorder characterized by AVMs mostly of the mucosa and viscera, but can also involve the skin.¹⁹ There are four subtypes of HHT, but only HHT1 and HHT2 will be discussed as they comprise ~85% of the cases.²⁶ HHT1 has been linked to a heterozygous mutation on chromosome 9q34, which contains the gene that encodes endoglin. HHT2 is caused by a mutation in ACVRL1 gene on chromosome 12q, which contains the ALK1 gene that codes for activin receptor-like kinase I, ACVRLK1.²⁷ Comparisons of HHT1 and HHT2 suggest that HHT1 has a higher incidence of pulmonary lesions; however, it should be noted that there is a great deal of phenotypic variability within each syndrome and clinically the forms are treated in the same manner.²⁸

A penetrance of 97% to 100% has been reported.^{29,30} Epistaxis is primarily the presenting symptom and 62% will manifest the disease by age 16 and 90% before age 21.³¹ Telangiectasias of the mucosa are most commonly located on the face, including the tongue, lips, conjunctiva, and nasopharynx.

In the viscera, various vascular malformations can occur, including arterial aneurysms, arteriovenous fistulas, and poorly formed masses of angiectasia, phlebectasia, and angioma.³² Pulmonary AVMs have been reported in 4.6% to 20% of cases and are associated with significant morbidity.^{29,33} These lesions can lead to massive hemorrhage, heart failure, and paradoxical emboli. Lesions within the liver are associated with pronounced fibrosis, which can progress to cirrhosis. One study found that 17 of 27 patients with hepatic involvement went on to develop cirrhosis.²⁹ The majority of neurologic symptoms are secondary to embolic phenomena, but vascular malformations can occur within the CNS, especially with HHT2.³²

Endoglin and activin receptor like kinase I are expressed within endothelium. These proteins are associated with transforming growth factor β (TGFB) receptor complexes. Endoglin is an accessory protein and activin receptor-like kinase is a transmembrane serine/threonine kinase.^{34,35} The many mutations described in HHT ultimately lead to a loss of

function of the TGFB signaling pathway.¹⁹ It is suggested that TGFB plays a role in the maintenance of the capillary bed as AVMs in HHT show a progressive disappearance of capillaries.³²

Lymphatic Malformations

Lymphatic malformations have the propensity to enlarge more than any other vascular malformation.³ They occur most commonly in the neck and axilla (55% to 95%).³ These lesions can often become infected, and if located in the head and neck, can compromise the airway. Primary lymphedema, also known as Milroy disease, is an autosomal dominant disorder caused by FL4 missense mutations on 5q35.3. This locale encodes for VEGFR3, and missense mutations here disrupt the kinase domain of the protein, disrupting signaling and ultimately leading to dysregulation of lymphatic endothelium development.³

Mixed Lesions

Klippel-Trenaunay Syndrome

Klippel-Trenaunay Syndrome (KTS) has been defined as slow flow, combined capillary, venous and lymphatic malformation involving the limb, or less frequently, the trunk. High-flow arteriovenous fistulas are absent or are a minor component, a key distinction from Parkes-Weber syndrome.³ The lower limb is involved in the vast majority of cases (95%); however, 15% of patients have combined upper and lower limb involvement.³ A study of 47 patients exhibited a 53% rate of thrombophlebitis and Kasabach-Merritt syndrome occurred in 45% of patients.³⁶ Other morbidities of the syndrome in this study included thromboembolism (11%) and high-output heart failure (13%).

The inheritance pattern as well as genes implicated in the pathogenesis of KTS is unclear. Some feel that it is a purely sporadic syndrome, while others have suggested that KTS is a paradominant trait, where the syndrome is linked to a single gene and heterozygotes develop an early somatic mutation, leading to mosaicism.^{3,37} With that in mind, no clear genetic basis for KTS has been found. Whelan et al reported a reciprocal translocation in a patient with KTS at t(5;11)(q13.3;p15.1) and suggested that the culprit gene was on 5q or p11.³⁸ Tian et al identified the VG5Q gene and showed that the translocation found by Whelan et al results in a threefold increase in gene expression.³⁹ The VG5Q protein is known to promote angiogenesis, and has been shown to directly bind endothelial cells and promote proliferation. Furthermore, a heterozygous glu133-to-lys substitution (E133K) has been found, which has been shown to increase the activity of VG5Q.³⁹ Several studies have shown, however, that the E133K substitution can exist in patients without KTS; therefore, the mutation is a polymorphism and does not directly cause KTS.^{40,41}

Parkes-Weber Syndrome

Although many feel that Parkes-Weber syndrome is clinically similar to KTS, there are several key differences. In Parkes-

Weber, the AVM is the major contributing anomaly, whereas lymphatic malformation, if present, is minor.³ Lesions are more diffuse in nature and have a rosy color. The upper limb is affected more often than KTS, and patients tend to have a worse prognosis, as their condition can be complicated by heart failure. As mentioned above, the RASA1 gene has been linked to both CM-AVM and Parkes-Weber syndrome.³ Eerola et al propose that Ras activity modulators could potentially serve as a targeted therapy for treatment of these patients.⁴²

Proteus Syndrome

Proteus syndrome is a severe disorder of variable phenotypes involving vascular/lymphatic malformation in addition to asymmetric and disproportionate growth of body parts, connective tissue, epidermal nevi, and adipose tissue.⁴³ Given the range of phenotypes possible in this disorder, it was aptly named after the Greek god Proteus, also known as “the polymorphous,” for his ability to change his shape to avoid capture.⁴⁴ Despite the many disparate phenotypes, several studies have sited both lipomatosis as well as hypertrophy of the skin of the soles as a unique feature of the syndrome,^{45–47} while it is the connective tissue nevi that are considered pathognomonic for diagnosis.⁴⁸

Proteus syndrome is rather uncommon, with an incidence of less than one case per million. And though most cases of Proteus syndrome are considered to be sporadic, reports of cases in monozygotic twins suggest familial transmission and in particular the concept of somatic mosaicism caused by a postzygotic mutation event.^{49,50} This is in support of the hypothesis that Proteus syndrome is caused by a somatic mutation, which is lethal when constitutive.⁵¹ Studies analyzing exon sequencing have also identified an activating missense mutation in the AKT1 gene.⁵² The AKT1 gene encodes for the enzyme RAC- α serine/threonine-protein kinase, which is catalytically inactive in fibroblasts and activated by platelet-derived growth factor. Ex vivo studies in cell culture have shown that prevalence of the mutation is higher in the upper dermis than in the epidermis or lower dermis and that the mutation is absent in glandular tissue, which may explain why certain cell types are more affected than others in this disorder.

Conclusion

The genetic basis for vascular malformations is incredibly complex. The great deal of phenotypic variability within known gene mutations suggests that we do not fully comprehend the exact genetic contribution to syndromes.¹⁴ However, further investigation will allow us to identify at-risk patients in the hopes of preventing the more severe sequelae of the syndromes. Furthermore, in-depth knowledge of the molecular basis of these lesions will provide ample opportunity to develop tissue-targeted therapy.

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