Familial Segregation of Hemangiomas and Vascular Malformations as an Autosomal Dominant Trait

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Background: The pathogenesis of infantile hemangiomas is not yet understood. Growth factors and hormonal and mechanical influences have been thought to affect the focal abnormal growth of endothelial cells in these lesions. However, these influences may represent secondary responses to an underlying primary molecular event leading to the development of hemangiomas.

Observations: We report the rare familial occurrence of hemangiomas and/or vascular malformations in 6 kindreds, suggesting autosomal dominant inheritance. In these families, multiple generations (2-4) were affected by hemangiomas or vascular malformations. In contrast to the generally accepted female-male ratio of 3:1 to 4:1 associated with sporadic hemangiomas, the families with hemangiomas in our study demonstrated a 2:1 ratio. Additionally, vascular malformations and hemangiomas were present in different members of the same family. The vascular lesions appeared to be transmitted in an autosomal dominant fashion with moderate to high penetrance.

Conclusions: We have identified 6 families demonstrating autosomal dominant segregation of childhood hemangiomas. Additionally, family members with vascular malformations were identified in these kindreds. Physicians caring for children with hemangiomas and vascular malformations should include in their medical histories inquiries about vascular lesions in other family members, even when obvious lesions are not present in the parents. The identification of the mutation(s) underlying vascular lesions will provide insight into the pathogenesis of these familial hemangiomas and, potentially, common sporadic hemangiomas. In addition, such research would shed light on the regulation of angiogenic processes during development.

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Hemangiomas, the most common type of tumor in infants, are benign localized growths of proliferating blood vessels that consist primarily of endothelial cells. Hemangiomas may be superficial, deep, or both and are most commonly located in the head and neck region. Although most infants exhibit only 1 hemangioma, 20% may develop multiple hemangiomas. A subset of these children with multiple hemangiomas have “diffuse neonatal hemangiomatosis” and are at risk of developing internal hemangiomas. Hemangiomas occur more frequently in females (female-male ratio, 3:1 to 4:1). They are usually self-limiting and go through a characteristic 2-staged process of growth and regression. The proliferation phase corresponds with a rapid period of growth of endothelial cells forming syncytial masses with and without lumens. This phase usually lasts from 6 to 12 months. Later, in the involution phase, fibrosis of the tissue increases, with a decreasing endothelial cell component and deposition of fibroadipose tissue. The involution phase usually begins spontaneously and can last for months or often years. Despite this clinical course, hemangiomas nonetheless may be the source of psychosocial morbidity (although this has not been well studied) and can compromise critical organ functions (eg, the airway and vision), requiring medical intervention.

The separation of vascular anomalies into proliferative lesions and static malformations represents an important advance, because the management of these 2 types of anomalies is very different. Whereas hemangiomas are proliferative vascular lesions that occur abruptly and exhibit the clinical course described above, vascular malformations are present at birth and grow proportionately with the rate of growth of the child, with no tendency for spontaneous involution. Vascular malformations may change in size in response to infection, trauma, or hormonal changes, but they are not proliferative.

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The pathogenesis of infantile hemangiomas is not yet understood. Recent immunohistochemical analyses of hemangiomas document a number of biochemical markers for the different phases of the development of hemangiomas. Proliferating cell nuclear antigen, vascular endothelial growth factor, and type IV collagenase.
METHODS

When documenting the medical histories of our pediatric patients with vascular anomalies, we inquired if other family members were affected by vascular lesions. Our categorization of the patients followed the classification scheme proposed by Mulliken and Glowacki. We defined as hemangiomas lesions that grew after birth or were present at birth and showed evidence of regression subsequent to infancy. Lesions that had been treated with liquid nitrogen (a treatment used on hemangiomas in the 1950s and 1960s) were also classified as hemangiomas. By contrast, vascular malformations were defined as lesions that were present at birth (or presumed to be so in the case of cerebral lesions) and did not undergo the progression and regression of hemangiomas or have the typical radiological appearance of vascular malformations.

For families with multiple members (from 2 or more generations) affected by hemangiomas, we obtained a thorough medical history from available family members to document the most accurate clinical history and description of their vascular lesions. All probands and immediate family members were also examined, and when possible, second- and third-generation family members also underwent examinations. When possible, photographs were obtained from the families or taken of the family members at the time of their medical examinations.

For family members affected by hemangiomas, we noted the type and distribution of their vascular lesions. The family pedigrees are shown in the Figure.

were detected solely in the proliferating phase, whereas basic fibroblast growth factor and plasminogen activator inhibitor of metalloproteinase was observed only in the involution phase. CD31, von Willebrand factor, and smooth muscle cell actin staining were present during the proliferation phase but increased during the involution phase. Fully involuted lesions showed markedly lower levels of staining for all 3 antigens. Martin-Padura et al demonstrated by immunohistochemical analysis the presence of normal endothelial and basement membrane markers in hemangioma tissue, suggesting that the abnormal growth seen in proliferating hemangiomas is related more to the local release of growth factors than to an altered endothelial phenotype. More recently, Berard and colleagues reported that human neonatal stromal hemangioma cells express vascular endothelial growth factor, which functions in an autocrine loop and as a paracrine factor for endothelial cells. These data provide some insight into the pathogenesis of hemangiomas, but the expression of growth factors and enzymes may be secondary responses to an underlying primary molecular event leading to the development of hemangiomas.

One approach to the identification of an underlying molecular event is to search for genetic alterations that may lead to the development of hemangiomas. However, there is a paucity of literature on the molecular genetic analysis of hemangioma tissue, and we are not aware of published descriptions of familial inheritance that might suggest predisposing genetic mutations. A recent review of the literature on genetics by Burns et al revealed that dysomorphic syndromes are more commonly associated with vascular malformations than with hemangiomas. Examples of these disorders are Sturge-Weber syndrome (associated with capillary malformation), Turner and Noonan syndromes (associated with lymphatic malformation), Klippel-Trenaunay syndrome (associated with capillary, venous, and lymphatic malformations), and blue rubber-bleb nevus syndrome (associated with venous malformations). On the other hand, dysmorphic syndromes associated with hemangiomas seem to be limited to variable forms of expression, including posterior fossa brain malformations, hemangiomas, arterial abnormalities, coarctation of the aorta, other cardiac defects, eye abnormalities, sternal clefting, and supraumbilical raphe (PHACES...
syndrome).²⁴ In contrast to several heritable vascular malformation syndromes (eg, hereditary hemorrhagic telangiectasia, cerebral vascular malformations, and mucocutaneous venous vascular malformations), syndromes associated with hemangiomas do not appear to be inherited. Interestingly, Gorlin et al²⁵ observed a marked female predilection in syndromes associated with facial hemangiomas that far exceeded the expected 3:1 to 4:1 female-male ratio.

We describe herein kindreds in which multiple members are affected by hemangiomas, apparently through autosomal dominant inheritance. Furthermore, we identify patients with hemangioma(s) who have relatives with vascular malformations.

**RESULTS**

We identified several families with multiple generations with infantile hemangiomas. Representative pedigrees and clinical descriptions of 6 of these families are listed below in more detail. The pedigrees are illustrated in the Figure. The appearance, location, and clinical courses of the hemangiomas in these families were indistinguishable from sporadic hemangiomas. Interestingly, in our families, the distribution of hemangiomas between sexes differed from the generally accepted female-male ratio of 3:1 to 4:1. In the pedigrees presented, the female-male ratio was 2:1. In addition to these families, we have identified several other families in which several members were affected by hemangiomas but not clearly with autosomal dominant segregation. This could be due to reduced penetrance in some of the family members. When we considered these families, the overall female-male ratio of family members with hemangiomas was 1.4:1.

**FAMILY 121**

A woman (I-2) had 6 hemangiomas (on her head, leg, and trunk). Four of her 5 children had hemangiomas. One of her daughters (II-2) had a large hemangioma on her forearm. That daughter had 1 son (III-1) who had a hemangioma on his cheek. Another daughter (II-4) of the propositus (I-2) had hemangiomas on her lip and groin. That daughter (II-4) gave birth to 2 children, one of whom (her son [III-3]) had a hemangioma. Another daughter (II-5) of the propositus had a hemangioma on her buttocks. She had no offspring. The propositus had 2 identical twin boys, one (II-7) who had a capillary malformation on his forearm (extending from just above the wrist to just below the elbow) and another (II-8) who had a hemangioma on his face and shoulder. One of these sons (II-7) had 3 children, one of whom (a daughter [III-6]) had hemangiomas on her head. The other twin son (II-8) had 2 sons, one of whom (III-8) had a hemangioma.

Thus, in this kindred, 3 successive generations were affected by vascular lesions, including both hemangiomas and vascular malformations. All 5 children of the propositus (I-2) had vascular lesions: 4 had hemangiomas, and 1 (an identical twin) had a capillary malformation. Four of the propositus' 8 grandchildren had hemangiomas. The female-male ratio of hemangiomas in this kindred was 1.25:1.

**FAMILY 129**

A woman (II-3) had a hemangioma on her back. Her niece (III-3) had a vascular lesion on her scalp. That niece (III-3) had 2 sons, one of whom (IV-1) had a hemangioma on his head. The unaffected son (IV-2) had 2 daughters, one of whom (V-2) had an extensive hemangioma on her buttocks, perineum, and leg. Thus, we were able to identify 4 generations of family members with hemangiomas in this kindred.

**FAMILY 130**

A man (II-1) had a port-wine stain (capillary malformation) on his hand. His wife (II-2) had a hemangioma on her head. Three of their 6 children had vascular lesions. One daughter (III-1) had a hemangioma on the anterior part of her chest; another daughter (III-2) had a lymphatic vascular malformation (cystic hygroma) on her neck; and another daughter (III-6) had a hemangioma behind her ear lobe.

**FAMILY 132**

A woman (I-2) had 2 or more small hemangiomas on her trunk. Of her 3 children, one son (II-3) had 3 or 4 hemangiomas on his chest and back. This son had 2 children with hemangiomas: a daughter (III-1) who had a single hemangioma on her nose, and a son (III-2) who had 1 large hemangioma on his back and 3 smaller hemangiomas on his chest, shoulder, and foot.

Thus, in this kindred, there were hemangiomas in 3 successive generations. Most of the affected individuals in this kindred exhibited multiple hemangiomas.

**FAMILY 133**

A man (I-1) had a capillary malformation on his neck. He had 3 children, 2 of whom (II-2 and II-5) had capillary malformations, and 1 of whom (III-3) had a hemangioma on her calf. One daughter (II-2) had 3 children, 1 of whom (III-2) had a hemangioma on her scalp. The man's other daughter (II-3) had 2 sons, 1 of whom (III-4) had a hemangioma on his eyelid. The other son (III-5) had a capillary malformation on his neck. One of the sons of I-1 (II-5) had 2 daughters (III-6 and III-7), both of whom had hemangiomas. One of those daughters (III-6) had a hemangioma on her back and neck, while the other (III-7) had a subglottic hemangioma.

**FAMILY 136**

A man (II-2) had a capillary malformation on his abdomen. He had a set of fraternal twins, one of whom (III-3) had a large capillary malformation over her lower face and neck. The twin brother (II-2) was unaffected. A female cousin (III-5) had a hemangioma on her forehead. III-3 had 2 offspring, a son (IV-3) who had a hemangioma on his cheek, and a daughter (IV-2) who had a hemangioma on her abdomen.

**ADDITIONAL KINDREDS**

We also identified families (not reported in this series) in which multiple members of 1 generation were af-
fected by similar vascular lesions. One girl had a large venous malformation on her knee. Her brother had a lesion similar in appearance on his chest wall. Similarly, a brother and sister in another family both had hemangiomas on their right cheeks. In some families, it appears that clear segregation of the same or similar phenotype (e.g., hemangioma) is a dominant trait. However, perhaps most interestingly, we noted that it was not uncommon for our patients with hemangiomas to have siblings and other relatives with vascular malformations (e.g., port-wine stains, lymphatic vascular malformations, or cerebral arteriovenous malformations). In addition to those described in the above pedigrees, we identified 2 children with hemangiomas who had relatives with vascular malformations: one child's mother had a cranial vascular malformation, and the other child's maternal aunt had a large port-wine stain on her face and neck. Furthermore, the parents of 2 patients with vascular malformations that resembled those related to Klippel-Trenaunay syndrome also had vascular malformations (the mother had a cerebral arteriovenous malformation, and the father had a port-wine stain on his face).

Although most hemangiomas occur sporadically or as part of pleiotropic syndromes, we identified a number of kindreds in which clear autosomal dominant segregation of hemangiomas and/or vascular malformations was evident. For other families, reduced penetrance may mask autosomal dominant segregation. Both males and females were affected in approximately equal numbers, with the trait passing through at least 3 generations. There was not sufficient documented medical history to determine if these lesions occurred in earlier generations. Both hemangiomas and vascular malformations were observed in the same kindreds in some cases (Figure) and sometimes in the same individual (data not shown), suggesting that although these lesions have different pathologic features and clinical courses, an underlying genetic influence may be common to both. In family 121, an obligate carrier of the predisposing gene had a vascular malformation (capillary malformation), yet his children and his mother had hemangiomas. Furthermore, his identical twin brother developed a hemangioma in infancy.

In our 6 family pedigrees, the female-male ratio of individuals with hemangiomas was 2:1. At least 1 case of male-to-male transmission was demonstrated. These data suggest that the genes predisposing to hemangiomas in these kindreds are not sex linked. Furthermore, although a female-male ratio of 3:1 to 4:1 has been reported for cases of sporadic hemangiomas, that ratio apparently did not apply to the families in our study. If we assume that the skewed sex ratio with respect to sporadic hemangiomas is the result of hormonal influences, it appears that in these families such an influence is less relevant than or at least partially overridden by a predisposing genetic mutation. There are apparently 2 cases of a skipped generation in these kindreds, suggesting that the predisposing mutation has a high but incomplete penetrance and exerts a major influence on the development of the lesions. In 2 individuals in family 121, multiple hemangiomas were present in the same individual, suggesting that the predisposing genetic factor has a strong influence on the formation of vascular lesions.

Cheung et al studied the genetic factors involved in hemangiomas in a cohort of 118 pairs of twins. There was no significant difference between the number of monozygotic and dizygotic twins with hemangiomas. These data indicate that for sporadic hemangiomas, germ line mutations are not significant predisposing factors. Findings from our examination of kindreds affected by hemangiomas and results from the twin study by Cheung et al suggest that familial forms of hemangiomas are rare. One explanation for this low population frequency may be that only specific germ line mutations in a small number of genes are capable of creating the hemangioma phenotype. There is a precedent for this hypothesis in the rare case of families with autosomal dominant venous malformations who harbor a specific kinase-activating arginine-to-tryptophan mutation in the Tie-2 receptor tyrosine kinase. Presumably, most other possible mutations in this gene would lower or destroy the function of kinases or proteins, which would therefore not lead to the phenotype for venous malformations. In support of this hypothesis, the inactivation of the Tie-2 receptor in mice leads to embryonic lethality in the homozygous state and an apparent lack of any discernible phenotype in the heterozygous state.

The apparent rarity of the families described herein may also be due in part to insufficient data, since it is not routine to ask about familial tendencies for hemangiomas or vascular malformations. In addition, hemangiomas disappear with age, so some individuals may not know or may never have been told that they had a lesion as an infant. Although we do believe that families with autosomal dominant vascular anomalies are uncommon, it is likely that other such families will be identified through careful patient inquiry. Therefore, physicians caring for children with hemangiomas and vascular malformations should include in their medical history inquiries about vascular lesions in other family members, even when obvious lesions are not present in the parents (their hemangiomas would have long since resolved).

Other vascular lesions that are considered nonhereditary show familial segregation in rare instances. For example, Pasyk et al describe 6 families with medial telangiectatic nevi affecting multiple generations, suggesting autosomal dominant inheritance, even though these lesions are not normally considered to be heritable. Ceballos-Quintal et al describe a patient with Klippel-Trenaunay-Weber syndrome whose mother had a large cutaneous vascular lesion on her back and whose maternal grandmother had early venous varicosities of the legs. These authors suggest that the relatives of the patient had phenotypes of milder vascular malformations. They propose that Klippel-Trenaunay-Weber syndrome may be transmitted via autosomal dominant inheritance with variable expressivity.

Although sporadic hemangiomas are undoubtedly caused by multiple factors (including environmental, hormonal, and/or mechanical influences), we believe that the identification of the gene(s) underlying the hemangioma phenotype in these families will shed light on the pathogenesis of sporadic hemangiomas and these rare familial
forms of autosomal dominant vascular anomalies. Mutations that pass through the germ line and predispose family members to develop hemangiomas may also contribute to the formation of sporadic hemangiomas. These somatic mutations, which occur during fetal development, may lead to clonal expansion of affected vascular tissue. Rapid proliferation may be due to release from growth inhibition by hormonal, immunological, and other changes shortly after birth. Alternatively, the gene products themselves may be deregulated or may otherwise play a role in the formation of lesions in sporadic hemangiomas. The identification of these genes and their gene products would therefore be invaluable to our understanding of the development of hemangiomas in particular, and more generally, the regulation of angiogenesis.

Venous malformations and hemangiomas have distinctly different clinical courses and a number of different pathologic characteristics. It is surprising that in some of our families, both types of vascular lesions were present in different individuals. This might indicate that although different, the development of both types of lesions may involve the deregulation of a common regulatory pathway. A number of tyrosine kinases and other growth regulatory molecules have been implicated in the processes of angiogenesis and vasculogenesis. A genetic linkage analysis of the families in our study and a candidate gene approach that considers these gene products might indicate whether any of these gene products play a role in the pathogenesis of venous malformations and hemangiomas.

Within the past several years, a genetic linkage approach has been successful in identifying specific genetic defects associated with certain inherited vascular anomalies. Two genes have been identified that are mutated in hereditary hemorrhagic telangiectasia, an autosomal dominant disorder of vascular dysplasia that includes the development of arteriovenous malformations. Endoglin is the gene for hereditary hemorrhagic telangiectasia 1 and a transforming growth factor β-binding protein found on endothelial cells. The activin receptor-like kinase 1 gene is mutated in a second form of hereditary hemorrhagic telangiectasia. Both gene products may be involved in vascular remodeling associated with transforming growth factor β. A mutation causing an activating mutation in the kinase domain of Tie-2 was recently reported in 2 families with multiple members that have mucosal venous vascular malformations. This mutation is thought to cause an abnormal interaction between endothelial cells and smooth muscle cells, leading to dilated venous channels surrounded by few smooth muscle cells. An inherited form of a cerebral cavernous malformation has been mapped to chromosome 7q.

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Douglas A. Marchuk, PhD, is an Established Investigator of the American Heart Association.

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REFERENCES

Correction

Error in Figure. In the observation titled “Familial Segregation of Hemangiomas and Vascular Malformations as an Autosomal Dominant Trait,” published in the June issue of the ARCHIVES (1998;134:718-722), one of the elements of the Figure was incorrectly presented; subject I-2 in family 121, who was affected, should have been represented with a darkened circle. The portion of the Figure concerning this family is reprinted correctly here. We regret the error.