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NEWS AND COMMENTARY

Vascular Pathologies

Angiogenomics: towards a genetic nosology and understanding of vascular anomalies

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Vascular lesions have acquired numerous names, many of which are eponymous, reflecting our ignorance of the underlying pathogenic mechanisms. Reading the literature, a clinician not familiar with the field can be easily overwhelmed and confused by the terminology. Fortunately, molecular genetics has begun to unravel the mysteries of vascular anomalies. Nevertheless, several factors have inhibited this development. In the past, the role of heredity was overlooked, mostly due to variation in expressivity, low penetrance, high frequency of phenocopies, and the localized nature of lesions. In addition, patients with vascular anomalies wonder among different specialties, thus decreasing the chance of noting that some of these disorders follow a Mendelian inheritance pattern. Finally, accurate phenotypic identification of patients is crucial for genetic research, and this only became possible after the fundamental work of Drs Mulliken and Glowacki,[1] which is the basis for clinically useful and simple classification of vascular anomalies, later adopted by the International Society for the Study of Vascular Anomalies (ISSVA), and clinicians and scientists in various fields. This classification divides vascular anomalies into tumors (infantile hemangiomas and other intermediate and high-grade malignancies) and malformations, which are subdivided into capillary, venous, lymphatic, and arteriovenous malformations. On the basis of this nosology, several genes in which mutations cause recessive and/or dominant forms of vascular anomalies have been identified.[2] Furthermore, recognition of genetic vascular disorders and molecular testing has helped in clinical practice to distinguish better similar looking lesions. This has paved the way for more precise diagnosis and clarification of the classification and fundamental basis for some vascular anomalies.

In an article entitled 'Angioma serpiginosum with esophageal papillomatosis is an X-linked dominant condition that maps to Xp11.3–Xq12', Ellen Blinkenberg *et al*[3] describe the identification of a locus for a rare cutaneous vascular anomaly. This discovery was based on careful clinical characterization of a single four generation family, in which four females had lesions similar to those previously named by Dr Hutchinson as *angioma serpiginosum*.[4] The lesions observed in the four affected family members are only partially blanched by compression, and histologically consist of increased number of dilated, thick-walled subepidermal capillaries. Similar vascular lesions that affect the subepidermal capillary network include, for example, (1) telangiectasias that vary from small punctate lesions to large geographic areas consisting of non-homogenously affected areas; (2) capillary malformations that can also be small or extensive, but which are usually more homogeneous, less bright in color, and darken with age; (3) atypical capillary malformations that are pinkish gray in color with a white halo, caused by a RASA1 mutation; and (4) faint capillary stains that can be encountered for example, as cutis marmorata telangiectatica congenita (CMTC) or associated with soft tissue and bony hypertrophy, such as in macrocephaly-capillary malformation (M-CM).[5] Because of the rarity of *angioma serpiginosum* and the limited number of affected individuals in the described X-linked family, it is impossible to say whether the lesions now described are the same as those defined by Hutchinson. On the basis of the clinical phenotype, the history of very slow progression of the lesions, and the presence of enlarged thick-walled capillaries in histological sections, the lesions in this X-linked family could be classified, following the ISSVA classification, under capillary anomalies or further defined as *progressive patchy capillary malformations*. Interestingly, as in many vascular syndromes, such as Parkes–Weber and Klippel–Trenaunay, lower extremities are more often affected in these patients.[6] There is no explanation for this predilection.

Faint vascular stains are often seen in patients with more severe medical problems that their presence fails to evoke great interest. This is illustrated in the present report, as the index patient's sister had been investigated for her papillomatosis, but no attention had been paid on her cutaneous vascular lesions. Later, the cutaneous stains suggested an inherited disorder, and this led to the identification of inherited papillomatosis in the family. Similarly, genetic knowledge has helped to establish other associations, such as hereditary hemorrhagic telangiectasia with juvenile polyposis, caused by mutations in SMAD4,[7] or the combination of atypical capillary malformations with fast-flow vascular anomalies in the capillary malformation-arteriovenous malformation disorder, caused by mutations in RASA1.[8] Additional associations may exist, as capillary malformations are common with varied presentation. Thus, the study of vascular anomalies not only gives knowledge on factors important for vasculogenesis and angiogenesis, but also clues to understand human pathology and genetic influence in a larger context.

This newly discovered locus on chromosome Xp11.3–q12 links cutaneous telangiectasias not only with esophageal papillomatosis, but also to minor nail and hair dystrophy. Thus, there is some

clinical resemblance with Goltz–Gorlin syndrome (focal dermal hypoplasia), which combines cutaneous rash and papillomatosis with dermal hypoplasia, herniation of fat and digital anomalies. Nevertheless, the three latter signs were not observed in the X-linked family. Interestingly, all affected individuals in the present family are women, with strongly skewed X-chromosome inactivation, suggesting a dominant X-linked disorder, incompatible with life in men. This is underscored by the few described men who have only segmental *angioma serpiginosum*. This fits with the current hypothesis of post-zygotic and/or somatic mutations being causative for some sporadic vascular anomalies. Interestingly, the more severe Goltz–Gorlin syndrome also affects predominantly women. Thus, it may be that the two conditions are allelic, caused by mutations of different severity.

The chromosome X-locus contains 275 genes, three interesting functional candidates, of which the authors have excluded as the site of the mutation. It remains to be seen, if this new angiogenic player has also pleiotrophic effects, involved in cell differentiation and apoptosis, as suggested by the authors. The other factors that cause vascular anomalies seem to affect cell surface growth factor receptors and their downstream signaling pathways that regulate apoptosis, differentiation, and proliferation. Once the gene is identified, it will be possible to study whether this X-linked factor is involved in the pathogenesis of some of the sporadic conditions thought to be due to mosaicism, such as Klippel–Trenaunay syndrome and capillary malformation associated with hypertrophy. Moreover, as hemangiomas are more frequent in female infants, and this tendency is even more marked in PHACES association[9] (posterior fossa brain malformation, large or complex hemangioma of the face, arterial anomaly, cardiac anomaly, eye abnormality and ventral developmental defects, such as sternal clefting or supraumbilical raphe), perhaps the factor causing the described inherited X-linked vascular anomaly is involved in the pathogenesis of these frequent vascular tumors as well■

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