COMMENTARY

Genetic understanding of vascular anomalies: better classification and risk-stratification with targeted therapeutic options – a new horizon for vascular anomaly patients

In the world of congenital vascular anomalies, as well as other congenital conditions, knowledge about the (genetic) causes of the disorders is developing fast.[1] Whereas in the past, clinical syndromes were distinguished on the basis of different sets of (major and minor) criteria,[2] whereby making an unambiguous diagnosis remained difficult, nowadays much more insight can be obtained through genetics.[3] Vascular anomalies are often sporadic (not familial) and concern an expression of a post-zygotic DNA mutation in somatic mosaic. Only a small portion of the vascular anomalies is familial and an expression of a germline-mutation.[3] It turns out that syndromes that were previously difficult to distinguish, are an expression of distinctive activating mutations in the same cellular pathway; for example Klippel-Trenaunay syndrome and Proteus syndrome, which are caused by a PIK3CA mutation and an AKT1 mutation, respectively, both mutations from the PI3K/AKT/mTOR pathway. On the other hand, it appears that one particular somatic mutation (in mosaic) can give a spectrum of clinical pictures, depending on the location, cell type and moment of mutation in the embryo phase. An example of this is the PIK3CA Related Overgrowth Spectrum, PROS.[4]

The above examples concern syndromes with low-flow vascular malformations. Similar processes go for high-flow vascular malformations as depicted in the article by El Sissy *et al.*[5] describing a group of patients with an extra-cranial arteriovenous malformation (AVM). Where the AVM is generally diagnosed with the physical and radiological examination, in the study by El Sissy *et al.* tissue was obtained as well from the patients. Histology is in general not an essential part of the diagnosis for vascular anomalies and is really only essential if a vascular tumour is suspected. But for insight into the genetics of vascular anomalies, tissue may also be needed, especially in sporadic cases. One can imagine that obtaining tissue in these types of high flow vascular anomalies is challenging, but also provides a lot of extra information.

This study by El Sissy *et al.* provides insight into the genetic cause of AVM in a relatively large group of patients. In addition to clinical/radiological classification systems, such as the Schöbinger- and Yakes-classification, genetic classification appears to provide important additional insight. For example, the course and clinical picture of AVMs with MAP2K1-mutations appear to be more favourable than those with KRAS mutations (100% relapse after surgery).[5]

It is useful to know that mutations seen in vascular malformations are analogous to mutations in oncological pathways; mutations in congenital conditions occur in the embryonic stage as opposed to oncological ones where they occur later in life.[1] For oncologic indications targeted medicines are increasingly being developed. This may also benefit vascular anomaly patients. So, in addition to the classification of vascular malformations, genetic diagnosis provides new options on the therapeutic ladder for vascular malformations: targeted therapy.[1] And that is a good thing, because the ladder for AVM may be disappointing; treatment with embolization is often a long-term process in which curation is unfortunately not always feasible. Surgery is also not always curative, especially not for large or unfavourably localized anomalies, as the article of El Sissy *et al.* shows as well.[5]

A possible bias in this study is that it all involved patients that received surgery as a treatment. Because the surgical excision specimen was the basis of the genetic research, it could just be that AVMs that cannot be treated surgically have a different (genetic) cause, whereby new groups of AVMs may eventually be distinguished. Nevertheless, this clinical-radiological-genetic correlation provides more insight into what is really going on and eventually results in a larger therapeutic arsenal, a favourable prospect, a new horizon for this patient group with often a high disease burden.

Conflicts of interest

The author has no conflict of interest to declare.

Funding sources

This article has no funding source.

Data availability statement

None

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Commentary to 'Somatic mutational landscape of extracranial arteriovenous malformations and phenotypic correlations' by F.N. El Sissy *et al*.

Linked article: F.N. El Sissy et al. *J Eur Acad Dermatol Venereol* 2022; **36**: 905–912. https://doi.org/10.1111/jdv.18046.

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DOI: 10.1111/jdv.18155