RASA1 Variants in Capillary Malformations of Children: A Comment to Maruani A et al.

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Maruani et al. (1) present the results of an extensive multicentre study including a cohort of 113 children whose legs were affected by one or more capillary malformations (CMs). These individuals were examined for the presence of germline *RASA1* variants. The authors avoid the term "mutations" because they are not sure whether the documented alleles are pathogenic. In 7 children they found heterozygosity for a *RASA1* variant. Maruani et al. (1) use the presently prevailing classification of the International Society for the Study of Vascular Anomalies (ISSVA) (2, 3). However, this nomenclature does not discriminate between CMs that have specifically different dermatological criteria (4).

Fig. 2 of the study presents 6 "examples of clinical characteristics". However, Fig. 2a–c shows neither naevus flammeus nor rhodoid naevi (capillary malformation-arteriovenous malformation; CM-AVM). In my opinion, the most likely diagnosis is naevus roseus. This clinical entity is now well-established in Europe (4–6), but is still disregarded in other regions of the world (2, 3). Its molecular cause is unknown, but mutations in *GNAQ*, *GNA11*, *AKT1* or *PIK3CA* have been excluded (personal communication: Veronica Kinsler, London, UK, 20 October 2017). Fig. 2d shows a "geographic-type CM" (3) that may represent a port-wine naevus of the Proteus type or the CLOVES type (4), or a port-wine naevus of a still unknown type. Hence, the authors are correct to doubt that the *RASA1* variant pL116V is a pathogenic mutation. Fig. 2e suggests a diagnosis of rhodoid naevi (CM-AVM) (4) because a faint anaemic halo surrounds the pink macule on the left thigh, whereas the large segmentally arranged macule on the right lower leg may be taken as an example of type 2 segmental mosaicism (7). Finally, the bilateral vascular stains shown in Fig. 2f can, in my opinion, not be classified, but a diagnosis of rhodoid naevi (CM-AVM) can be excluded.

From a genetic point of view, when the underlying gene causing naevus roseus is determined, the children in Fig. 2a-c should be tested for a mutation in this gene. The underlying gene will almost certainly be elucidated in 2018. The girl in Fig. 2d should be tested for the presence of a *PIK3CA* or *AKT1* mutation. Moreover, the girl in Fig. 2e should be tested for an *EPHB4* mutation (8, 9), as already proposed by the authors.

In conclusion, the large-scale molecular study of CMs presented by Maruani et al. (1) shows that focusing on a single gene, such as *RASA1*, will yield less specific results. As an initial step, it may be preferable to categorize CMs according to their dermatological criteria, which would simplify the search for the molecular basis of a given disorder.

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The authors of the original article (Maruani et al.) were given the opportunity to comment in response to this Correspondence, but chose not to do so.

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