RASA1: variable phenotype with capillary and arteriovenous malformations

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Capillary malformation-arteriovenous malformation (CM-AVM) is a newly discovered hereditary disorder. Its defining features are atypical cutaneous multifocal capillary malformations often in association with high-flow lesions: cutaneous, subcutaneous, intramuscular, intraosseous and cerebral arteriovenous malformations and arteriovenous fistulas. Some patients have Parkes Weber syndrome — a large congenital cutaneous vascular stain in an extremity, with bony and soft tissue hypertrophy and microscopic arteriovenous shunting. In the past, arteriovenous malformations and arteriovenous fistulas had been considered non-hereditary. A classical genetic approach was used to identify the locus. Candidate gene screening pinpointed mutations in *RASA1* (p120-RASGAP) — a RasGTPase. RASA1 reverts active GTP-bound Ras into inactive GDP-bound form. Murine *Rasa1* knockout and tetraploid-aggregated embryos with RNA interference exhibited abnormal vascular development. Lack of RASA1 activity caused inhibition of cell motility, possibly through p190-RhoGAP. Thus, RASA1 defects probably cause abnormal angiogenic remodeling of the primary capillary plexus that cannot be compensated for by other RasGAPs: RASA2, RASAL and NF1. Signaling pathways involving RASA1 might offer novel targets for treatment of high-flow vascular anomalies.

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Introduction

Vascular malformations are localized developmental lesions that can involve any organ system but are most easily seen on the skin [1]. Although many vascular anomalies are harmless, others cause major functional problems or death. Vascular malformations are considered to be defects of angiogenic remodeling of the primary capillary plexus [2]. These lesions are divided into four major categories on the basis of clinical, rheological and histological and/or immunohistological features: capillary, lymphatic, venous and arteriovenous malformations [3].

Vascular malformations have several features of potential heuristic value. Most importantly, they are nearly always localized (i.e. the majority of vessels are normal and the malformed vessels arise in a limited area). Although the majority of vascular malformations do not seem to be inherited in a Mendelian way, numerous families with autosomal dominant inheritance have been reported [2]. Interestingly, sporadic lesions tend to be single and large whereas familial lesions are often small and multifocal [4•]. Additionally, in the families with hereditary predisposition, there is wide clinical variability and high penetrance (around 90%). Expressivity varies from small harmless lesions to large symptomatic ones [4•]. Moreover, it is the location of the lesion, rather than its size, that determines morbidity.

Genes for several vascular anomalies have been identified: *TIE2* receptor tyrosine kinase for mucocutaneous venous malformation (VMCM; Online Mendelian Inheritance in Man (OMIM) 600195) [5]; glomulin for glomuvenous malformation (GVM; OMIM 138000) [6]; *KRIT1* (*Krev1 interaction trapped 1*), malcavernin and programmed cell death 10 (*PDC10*) for cerebral cavernous malformation (CCM; OMIM 116860, 603284, 603285) [7,8••,9••]; endoglin and activin-like kinase for hereditary hemorrhagic telangiectasia (HHT; OMIM 187300, 600376) [10,11]; and *MADH4* for juvenile polyposis associated with HHT (JPHT; OMIM 175050) [12•]. All mutations, except those in *TIE2*, are thought to cause loss of function. *TIE2* mutations confer increased phosphorylation of the receptor and, thus, result in gain of function. All these mutations cause vascular defects that seem to be inherited as an autosomal dominant disorder. However, a somatic second-hit has been observed in the glomulin gene responsible for multiple GVMs, which suggests that paradominant inheritance (see Glossary) might explain their localized nature [2,13]. Reports for CCMs do not support this mechanism [14,15]; perhaps these lesions are caused by mutations in two different underlying genes (i.e. somatic transheterozygosity; see Glossary) (N Revencu and M Vikkula, unpublished).

CM-AVM is a similar, newly identified vascular disorder [16••]. Here, we discuss its phenotypic variations, differ-

Glossary
Doppler – A method of ultrasonography to measure flow.
Hemiparesis – One-sided paralysis.
Paradominant inheritance – Pathology caused by the combination of a germ line and a postzygotic mutation.
Sequelae – The secondary alterations caused by a lesion.
Somatic transheterozygosity – Somatic mutation in paradominant inheritance occurs in different sites of the same gene or in a gene other than the one with a germ line mutation.
Vascular steal – High-flow with direct arterio-venous shunting, without passage through capillary beds, such that involved tissues are ischemic.

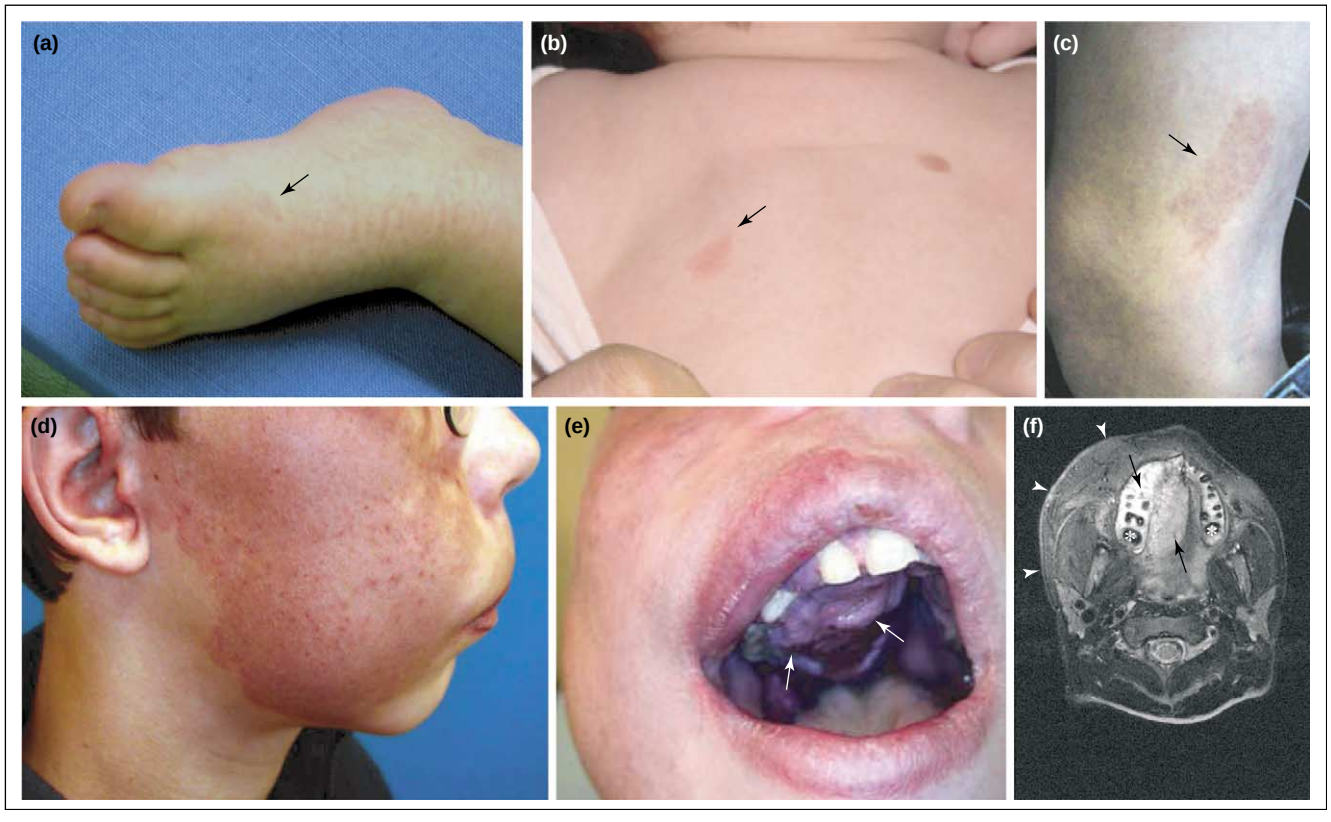
ential diagnosis and the molecular effects of the causative mutations on the function of RASA1.

Capillary malformation-arteriovenous malformation phenotype

The hallmark of CM-AVM is a small, round-to-oval, pink-red CM, typically multiple and in a haphazard distribution (Figure 1) [16••,17•]. In the six identified families, 39 individuals carried a *RASA1* mutation: four of them were unaffected, 25 had atypical CMs and 10 had a high-flow lesion in addition to the atypical CMs: two localized cutaneous and subcutaneous facial AVMs (one nasal and one frontal); one subcutaneous and intramuscular AVM of the foot; two extensive hemifacial AVMs with intraosseous involvement (Figure 1); two cerebral AVMs causing epilepsy in one patient, and hemiparesis (see Glossary) and congestive heart failure in another; Parkes Weber syndrome (OMIM 608355); and a carotid-jugular arteriovenous fistula (AVF) causing heart failure and hemifacial hypertrophy. Although four of the six families were identified in Belgium, we suggest that CM-AVM is likely to be a relatively frequent genetic disorder, because several clinicians have contacted us about suspected CM-AVM patients. It is not yet known whether all these patients have the same entity — a Ras p21 protein activator 1 (RASA1) mutation; there could be locus heterogeneity.

This newly described entity raises several interesting questions. What is the prevalence of CM-AVM? Is there genetic predisposition to AVM, a lesion once thought to be sporadic? Is there a predilection for localization of AVM or AVF in CM-AVM? Do patients with AVMs and AVFs with CM-AVM differ from patients with AVMs and

Figure 1



Photographs of capillary malformation-arteriovenous malformations (CM-AVMs). **(a)** Small, oval, pink-red CM of foot. Note narrow white halo (arrow). **(b)** Small, reddish, oval CM on thorax (arrow). **(c)** Larger, red-purple CM of lateral leg above knee (arrow). **(d)** Extensive red geographic, hemifacial CM-AVM (by palpation of the lesion, the skin is warmer on the lesion than on the contralateral side, but no thrill, owing to fast flow). **(e)** With palatal (arrows) and maxillary hypertrophy causing dental malalignment. **(f)** Magnetic resonance imaging (MRI) showing bony AVM (arrows) and soft tissue hypertrophy (arrowheads). Maxillary teeth (asterisks). (d–f) Same patient.