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Year: 2014

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DOI: <https://doi.org/10.1684/ejd.2014.2280>

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ZORA URL: <https://doi.org/10.5167/uzh-100460>

Journal Article

Accepted Version

Originally published at:

Feldmeyer, L; Baumann-Vogel, H; Tournier-Lasserre, E; Riant, F; Jung, H H; French, L E; Kamarashev, J (2014). Hyperkeratotic cutaneous vascular malformation associated with familial cerebral cavernous malformations (FCCM) with KRIT1/CCM1 mutation. *European Journal of Dermatology*, 24(2):255-257.

DOI: <https://doi.org/10.1684/ejd.2014.2280>

## **Hyperkeratotic cutaneous vascular malformation associated to cerebral cavernoma with KRIT1 mutation**

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Number of words: 861 (without abstract)

Number of tables: 0

Number of figures: 2

Number of references: 9

Funding sources: none

Conflict of interest: none

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Key words: cerebral cavernoma, KRIT1, cutaneous vascular malformation

Abbreviations: FCCM: Familial cerebral cavernous malformations; HCCVM: hyperkeratotic cutaneous capillary venous malformations; QMPSF: Quantitative Multiplex PCR of Short Fragments

## **ABSTRACT**

Familial cerebral cavernous malformations (FCCM) are vascular malformations inherited as an autosomal-dominant condition. Mutations in three genes have been described so far. Extra-neurological involvement includes retinal and cutaneous vascular malformations. Hyperkeratotic cutaneous vascular malformations are considered specific for FCCM and are always associated to KRIT1/CCM1 mutations. We report the case of a 40-years-old male patient with multiple cerebral cavernomas presenting with an asymptomatic isolated hyperkeratotic well-demarcated dark-blue plaque of ca. 0.5x1cm diameter on the left heel. Histologic examination showed a superficial, verrucous haemangioma with verrucous hyperorthokeratosis, slight papillomatosis and acanthosis of the epidermis as well as multiple strongly dilated thin-walled vessels in the superficial dermis. Based on these findings, a case of FCCM was suspected and mutation analysis was performed, which revealed a mutation in the exon 12 of KRIT1 (c.1201C>T).

## **INTRODUCTION**

Cavernous vascular malformations affecting about 0.5 percent of the population worldwide can occur anywhere in the body, but produce serious signs and symptoms only when they occur in the central nervous system. Patients with cerebral cavernous malformations may experience headaches, seizures, paralysis, hearing or vision deficiencies, and cerebral haemorrhage. The location and number of cerebral cavernous malformations determine the severity of this disorder. Approximately 25% of individuals with cerebral cavernous malformations never experience any related medical problems.

Familial cerebral cavernous malformations (FCCM) are inherited as an autosomal-dominant condition. Mutations in three genes (KRIT1 /CCM1, MGC4607/CCM2 and PDCD10/CCM3) account for 70 to 80% of all cases of familial cerebral cavernous

malformations. The remaining 20 to 30% of cases may be due to unidentified genes or to other unknown causes. The precise functions of the so far identified genes are not fully understood, but they most likely play a role in embryonic angiogenesis. Extra-neurological involvement in patients with FCCM includes retinal and cutaneous vascular malformations. Cutaneous involvement is seen in 9% of FCCM patients. Hyperkeratotic cutaneous vascular malformations are considered specific for FCCM and are always associated to KRIT1/CCM1 mutations. Dermatologists should be aware of this entity, since they can play an important role in identifying discrete but typical skin changes, leading to identification of the causing mutation.

## CASE REPORT

We report the case of a 40-years-old male patient with seizures since the age of 14 due to multiple cerebral cavernomas, treated by oxycarbazepine. Familial history for cerebral cavernomas was negative, but an uncle was known for a "brain tumor" (no exact medical diagnosis available), and the grandmother as well as the nephew of the patient had suffered a stroke. The patient was referred to the department of Dermatology by his neurologist for the evaluation of a dark-blue spot on the left heel, which had been present for many years. The lesion presented clinically as an asymptomatic isolated hyperkeratotic well-demarcated plaque, dark-blue in the centre with a reddish border, measuring ca. 0.5x1cm diameter (Figure 1). Histologic examination showed a superficial, verrucous haemangioma with verrucous hyperorthokeratosis, slight papillomatosis and acanthosis of the epidermis as well as multiple strongly dilated thin-walled vessels in the superficial dermis (Figure 2a). The vessels stained positive for the endothelial cell marker CD31 (Figure 2b) but were negative for the lymphatic endothelial cell marker D2-40 (Figure 2c). Based on these findings, we suspected a FCCM and performed a mutation analysis on the 16 coding exons of the KRIT1 gene by sequencing and QMPFS, revealing a mutation in the exon 12 (c.1201C>T) leading to the replacement of a glutamine by a stop codon at position 401 (p.Q401X), typical of those found in cavernoma (Florence Riant: found in how many% of patients?). The lesion did not disturb the patient, so it was not completely excised. The mutation analysis was followed by genetic counselling; indeed, the autosomal transmission implies a 50% risk for the children of the patient to inherit the mutation and a higher relative risk to develop cerebral cavernomas compared to the general population, although the penetrance is incomplete. A preimplantation genetic testing can be proposed to the affected patients.

## DISCUSSION

Cerebral cavernomas are vascular malformations of the central nervous system characterized by enlarged capillary cavities without intervening brain parenchyma. The prevalence in the general population is estimated as 0.1-0.5%, with familial incidence close to 20%.<sup>1</sup> Three CCM genes have been identified so far (*KRIT1/CCM1*, *MGC4607/CCM2*, *PDCD10/CCM3*).

The association between cavernous haemangiomas of the retina and brain with vascular lesions of skin has been reported in the literature since 1971,<sup>2-5</sup> but the responsible mutations has been first identified since 1999.<sup>6-8</sup> A series analysis of 417 patients revealed cutaneous vascular malformations in 9% of cases, including 15 hyperkeratotic cutaneous capillary venous malformations (HCCVM, 39%), 13 capillary malformations (34%), 8 venous malformations (21%) and 2 unclassified lesions. All patients with HCCVM had a *KRIT1/CCM1* mutation and *CCM1* was the most frequently mutated gene in cutaneous vascular malformations-FCCM patients.<sup>9</sup> This case illustrate the important role the dermatologist can play in identifying discrete but typical skin changes, leading to identification of the causing mutation.

## **FIGURES LEGENDS**

Figure 1:

Well demarcated verrucous plaque on the left heel of the patient

Figure 2:

Histological findings: Hyperkeratosis and numerous dilated capillary and venous vessels in the upper dermis seen in the hematoxylin-eosin stain (a). The dilated vessels are highlighted in the CD31 stain (b), but are negative for the lymph-vessel marker D2-40 (c).

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**Figure 1**



**Figure 2**

