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Cutaneous vascular anomalies associated with mosaic variant in *AKT3;* Genetic analysis continues to refine diagnosis, nomenclature, and classification of vascular anomalies

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To The Editor,

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Cutaneous vascular anomalies can be isolated or part of a spectrum of multi-system disorders. Antiquated nomenclature and complex classification schemas have created diagnostic confusion and impeded the development of screening guidelines. Next-generation sequencing (NGS) has become an important tool in investigation of vascular anomalies, allowing for improved molecular characterization, diagnosis, and identification of new pharmacologic therapies. We present three patients harboring a mosaic *AKT3* p.E17K variant in a cutaneous vascular anomaly reminiscent of cutis marmorata telangiectatica congenita (CMTC), two with associated megalencephaly (previously reported);[1,2] highlighting the genetic and phenotypic heterogeneity of cutaneous vascular disorders (Table 1, Figure 1, Supplemental Figs 1, 2).

There are many terms used for cutaneous vascular anomalies. Most experts use “capillary malformation (CM)” to describe pink-red, patches. Terms like diffuse and reticulated have been introduced to describe poorly delineated, lacey vascular anomalies. CMTC presents with unique patterns of coarsely reticulated, marbled, purple-red patches often with skin and subcutaneous atrophy. For those with associated macrocephaly, the term “Macrocephaly-Cutis Marmorata Telangiectatic Congenita” was initially introduced. However, Wright et al noted that these children had a distinct clinical appearance (less coarse and lacking atrophy) than other children with “true” CMTC and called for the renaming to Macrocephaly-Capillary Malformation (M-CM) syndrome.[3] They concluded that this anomaly was more consistent with reticulated CMs than CMTC.3 The acceptance of M-CM indicated that megalencephaly is not a feature of CMTC.[3]

We provide the first description of the skin findings in patients with the mosaic *AKT3* p.E17K variant. These patients’ cutaneous vascular anomalies were reminiscent of CMTC, but were more sharply-delineated, and linear located on lateral torso or extremity (Figure 1, Supplemental Figs 1, 2). NGS has demonstrated that a majority of patients with MCAP/M-CM have mosaic or constitutional variants in *PIK3CA*.[4] Like *PIK3CA*, *AKT3* signals through the PI3K/AKT/mTOR pathway and plays a key role in various cellular processes including cell proliferation and survival. The replacement of a glutamic acid by a lysine at amino acid 17 (*AKT3 p.E17K*) is believed to result in constitutive activation of AKT which results in increased AKT phosphorylation modulating downstream pathway activity.[1,2] Variants in *AKT3* p.E17K have been detected in megalencephaly and were detected in the brain tissue of two of these patients (Table 1).[1,2,4] Existing terminology fails to capture this phenotype. This cohort further illustrates that cutaneous vascular anomalies show significant overlap. Thus, we propose “*AKT3*-associated capillary malformation” for this clinical presentation.

Genotyping alone, should not be used to predict a phenotype. The timing of mosaic variants during embryogenesis and their distribution among cell lines dictates the extent of non-cutaneous disease. This series challenges the concept that one specific morphology of cutaneous vascular anomalies predicts risk for megalencephaly and expands this phenotype to include atrophic linear and stellate vascular anomalies. Cutaneous vascular anomalies with megalencephaly can be caused by a variety of constitutional or mosaic variants in *PIK3CA* and *AKT3*.[1,2] Patients with cutaneous vascular anomalies reminiscent of CMTC

should be monitored for megalencephaly following standard pediatric guidelines for head circumference measurements and molecular profiling should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

CMTC	Cutis Marmorata Telangiectatica Congenita
M-CM	Macrocephaly-Capillary Malformation
M-CMTC	Macrocephaly-Cutis Marmorata Telangiectatic Congenita
CM	Capillary Malformation
NGS	Next-generation sequencing

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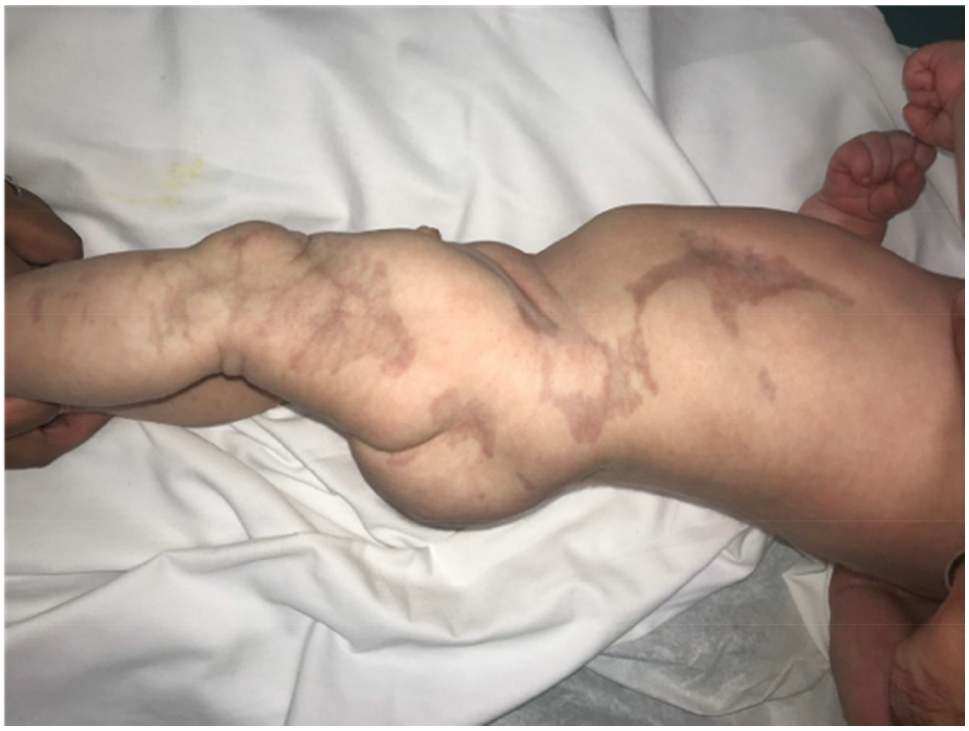

Figure 1: Representative Patient Phenotype

Patient #1: Photo taken at 2 months, male with deep red purple, coarsely reticulate and linear vascular anomaly with underlying skin atrophy. Proposed diagnosis of AKT3-associated capillary malformation.

Table 1:

Patient Descriptions and Genotype

Patient	Description	Brain MRI	*AKT3 p.* E17K Variant Allele Frequency/ Fraction	Genotyping Methods
1	Well-appearing 6-month-old male with a well-delineated red-purple linear and stellate depressed plaque with atrophy of the underlying subcutaneous dermis and fat on the lateral left torso, left buttock, and left lateral thigh.	Not Performed; Neurodevelopment normal	Skin: 4.60%	Clinical laboratory testing by NGS panel enriched for 177 target loci representing genes associated with cell signaling and cancer.[5]
2 #	Newborn male with seizures and a red-pink, well-delineated stellate patch with underlying soft tissue atrophy extending from the mid-lateral thigh to the dorsal aspect of the left foot. Patient underwent therapeutic hemispherectomy. Clinical hypotonia.	Hemimegalencephaly with contralateral hemimicroencephaly	Skin: 8.6–9.5% Brain: 12.6–13.9%	Brain tissue and skin fibroblasts cultured from perilesional skin underwent sequencing as described in Alcantara et al: LR15–262.[2]
3 #	Newborn female with seizures, retinal dysplasia and glaucoma of the left eye, and a red-purple well-delineated, linear and stellate patch on the left lower leg and back. Patient underwent a therapeutic left hemispherectomy. Clinical hypotonia.	Dysplastic megalencephaly	Skin: 1.3% Brain: 10–18%	Brain tissue and skin fibroblasts cultured from perilesional skin underwent sequencing as described in Jansen et al[1] and Alcantara et al: LR11–443.[2]

#Denotes patients previously reported in the literature[1,2]