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LETTER

RESEARCH LETTER

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

To the Editor: Cutaneous vascular anomalies can be isolated or part of a spectrum of multisystem disorders. Antiquated nomenclature and complex classification schemas have created diagnostic confusion and impeded the development of screening guidelines. Next-generation sequencing has become an important tool for the investigation of vascular anomalies, allowing for improved molecular characterization, diagnosis, and identification of

new pharmacologic therapies. We present 3 patients harboring a mosaic *AKT3* p.E17K variant resulting in a cutaneous vascular anomaly reminiscent of cutis marmorata telangiectatica congenita (CMTC), 2 with associated megalencephaly (previously reported),^{1,2} highlighting the genetic and phenotypic heterogeneity of cutaneous vascular disorders (Table I, Fig 1, Supplemental Figs 1 and 2 [available via Mendely at <https://data.mendeley.com/datasets/9wbr9sd2w6/1.>])

There are many terms used for cutaneous vascular anomalies. Most experts use “capillary malformation” to describe pink-red patches. Terms such as *diffuse* and *reticulated* have been introduced to describe poorly delineated, lacey vascular anomalies. Patients with CMTC present with unique patterns of coarsely

Table I. Patient descriptions and genotype

| Patient | Description | Brain MRI | <i>AKT3</i> p.E17K variant allele frequency/fraction | Genotyping methods |
|---------|---|--|--|---|
| 1 | Well-appearing 6-month-old infant with a well-delineated, red-purple, linear, stellate, depressed plaque, with atrophy of the underlying subcutaneous dermis and fat on the left side of the lateral aspect of the torso, left side of the buttock, and left side of the lateral aspect of the thigh. | Not performed; neurodevelopment was normal | Skin: 4.6% | Clinical laboratory testing by an 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 portion of the thigh to the dorsal aspect of the left foot. The 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 by Alcantara et al ² : LR15-262. |
| 3* | Newborn female with seizures, retinal dysplasia, and glaucoma of the left eye and a red-purple, well-delineated, linear, stellate patch on the left side of the lower portion of the leg and back. The patient underwent 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 by Jansen et al ¹ and Alcantara et al ² : LR11-443. |

MRI, Magnetic resonance imaging; NGS, next-generation sequencing.

*Denotes patients previously reported in the literature.^{1,2}



Fig 1. Representative patient phenotype. Photograph of a male infant (Patient 1) taken at 2-months-old demonstrating a deep red-purple, coarsely reticulated, linear vascular anomaly, with underlying skin atrophy. The diagnosis of *AKT3*-associated capillary malformation was proposed.

reticulated, marbled, purple-red patches, often with skin and subcutaneous atrophy. For those with associated macrocephaly, the term “macrocephaly-cutis marmorata telangiectatica congenita (M-CMTC)” was initially introduced. However, Wright et al³ noted that these children had a distinct clinical appearance (less coarse and lacking atrophy) compared to other children with “true” CMTC and called for M-CMTC to be renamed to macrocephaly-capillary malformation syndrome. They concluded that this anomaly was more consistent with reticulated capillary malformations than with CMTC.³ The acceptance of macrocephaly-capillary malformation syndrome (also called megalencephaly-capillary malformation syndrome) indicated that megalencephaly is not a feature of CMTC.³

To our knowledge, we provide the first description of 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, linear, and located on the lateral side of the torso or extremity (Fig 1, Supplemental Figs 1 and 2).

Next-generation sequencing has demonstrated that a majority of patients with macrocephaly-capillary malformation/megalencephaly-capillary malformation have mosaic or constitutional variants in *PIK3CA*.⁴ Like *PIK3CA*, *AKT3* signals through the phosphoinositide 3-kinase/serine/threonine protein kinase/mammalian target of rapamycin pathway and plays a key role in various cellular processes, including cell proliferation and survival. The replacement of glutamic acid by lysine at amino acid 17 (*AKT3* p.E17K) is believed to result in the

constitutive activation of AKT, which results in increased AKT phosphorylation modulating downstream pathway activity.^{1,2} Variants of *AKT3* p.E17K have been detected in patients with megalencephaly and were detected in the brain tissue of 2 of these patients (Table I).^{1,2,4} The existing terminology fails to capture this phenotype. This cohort further illustrates that cutaneous vascular anomalies show a 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 noncutaneous disease. This series challenges the concept that 1 specific morphology of cutaneous vascular anomalies predicts the risk of 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 of *PIK3CA* and *AKT3*.^{1,2} Patients with cutaneous vascular anomalies reminiscent of CMTC should be monitored for megalencephaly by following the standard pediatric guidelines for head circumference measurements, and molecular profiling should be considered.

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Conflicts of interest

Dr Garzon is an investigator for NCT02913612 Pediatric Trials Network-NIH Efficacy, Safety and Pharmacokinetics of Topical Timolol in Infants with Infantile Hemangioma (IH) (TIM01). Dr Frieden is a member of the Venthera Clinical Advisory Board, Pfizer (Data Safety Monitoring Board), and Novartis (consultant) and an investigator for NCT02913612 Pediatric Trials Network-NIH Efficacy,

Safety and Pharmacokinetics of Topical Timolol in Infants with Infantile Hemangioma (IH) (TIM01). Dr Saneto is an investigator for 5R01 NS092772-02. Dr Drolet reports an investigator-initiated trial funded by Pierre Fabre, Venthera consultant and Clinical Advisory Board member, she is the founder of Peds Derm Development, LLC, and is an investigator for NCT02913612 Pediatric Trials Network-NIH Efficacy, Safety and Pharmacokinetics of Topical Timolol in Infants with Infantile Hemangioma (IH) (TIM01). Drs Cottrell, Gripp, Shwayder, Mirzaa, and Davies have no conflicts of interest to declare.

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