PIK3CA gene mutation

Gain-of-function PIK3CA pathogenic variants have been identified in overgrowth syndromes collectively termed “PIK3CA-related overgrowth spectrum” (PROS). There are no previously reported cases of cerebrovascular venous malformations in PROS syndromes, though somatic activating PIK3CA variants have been identified in extracranial venous malformation. This study was approved by the Institutional Review Board at Boston Children's Hospital. A 14-year-old female mosaic for the de novo p.R108H pathogenic variant in the PIK3CA gene was found to have a large tumor involving the superior sagittal sinus with mass effect on the motor cortex most consistent with a parafalcine meningioma. She underwent surgical resection with pathology demonstrating a venous malformation. PIK3CA pathogenic variants have been identified in nonsyndromic extracranial venous and lymphatic malformations as well in brain tumors, including glioma and meningioma. However, PIK3CA variants have not previously been identified in purely intracranial venous malformations. This distinction is relevant to treatment decisions, given that mTOR inhibitors may provide an alternative option for noninvasive therapy in cases of suspected venous malformation [1].

Cerebral Cavernous Malformation CCMs arise due to loss of function in one of the genes that encode the CCM complex, a negative regulator of MEKK3-KLF2/4 signaling in vascular endothelial cells. Gain-of-function mutations in PIK3CA (encoding the enzymatic subunit of the PI3K (phosphoinositide 3-kinase) pathway associated with cell growth) synergize with CCM gene loss-of-function to generate rapidly growing lesions [2].

PIK3CA gene mutations cause cells to grow uncontrollably, which can lead to cancer. PIK3CA gene mutations are linked to breast cancer, as well as to cancers of the ovary, lung, stomach, and brain. Breast cancer likely stems from a combination of changes to PIK3CA and other genes.

Cerebral cavernous malformations (CCMs) arise owing to inactivation of the endothelial CCM protein complex required to dampen MEKK3 activity [3]

High-grade glioma (HGG) rarely spreads outside the CNS. To test the hypothesis that the lesions were metastases originating from an HGG, Marinari et al. sequenced the relapsing HGG and distant extraneural lesions.

They performed whole-exome sequencing of an HGG lesion, its local relapse, and distant lesions in bone and lymph nodes.

Phylogenetic reconstruction and histopathologic analysis confirmed the common glioma origin of the secondary lesions. The mutational profile revealed anIDH1/2 wild-type HGG with an activating mutation in EGFR and biallelic focal loss of CDKN2A (9p21). In the metastatic samples and the local relapse, they found an activating PIK3CA gene mutation, further copy number gains in chromosome 7 (EGFR), and a putative pathogenic driver mutation in a canonical splice site of FLNA.

The findings demonstrate tumor spread outside the CNS and identify potential genetic drivers of metastatic dissemination outside the CNS, which could be leveraged as therapeutic targets or potential biomarkers [4].

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