PIK3CA-related overgrowth spectrum

Gain-of-function PIK3CA pathogenic variants have been identified in overgrowth syndromes collectively termed “PIK3CA-related overgrowth spectrum” (PROS).

PIK3CA-related overgrowth spectrum (PROS) is an umbrella term for rare syndromes characterized by malformations and tissue overgrowth caused by somatic mutations in the PIK3CA gene. In PROS diseases individual malformations are seen in several different tissues such as skin, vasculature, bones, fat, and brain tissue depending on the specific disease.

As PIK3CA mutations are frequent events in lipomatosis of nerve, irrespective of anatomic site or territory overgrowth, Blackburn et al. proposed that all phenotypic variants of this entity be classified within the PIK3CA-related overgrowth spectrum and termed “PIK3CA-related lipomatosis of nerve” [1)]

PROS spectrum diseases include:

Fibroadipose hyperplasia or Overgrowth

Hemihyperplasia Multiple Lipomatosis

Congenital Lipomatous Overgrowth

Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal (CLOVES) syndrome

Macrodactyly

Facial Infiltrating Lipomatosis

Megalencephaly - Capillary Malformation

Dysplastic Megalencephaly

Klippel-Trenaunay syndrome

Treatment

Treatment of PROS diseases is variable and depends on the specific disease. Curative treatment does not exist and most treatments are given to control symptoms. Overgrowth and malformations of solid tissues can be treated with surgery. Sclerotherapy can be used to treat vascular malformations. In CLOVES syndrome experimental medical therapy using PIK3CA inhibitor, BYL719, has been reported to be effective to relieve pain and diminish malformations.

Case reports

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 [2].

1)
Blackburn PR, Milosevic D, Marek T, Folpe AL, Howe BM, Spinner RJ, Carter JM. PIK3CA mutations in lipomatosis of nerve with or without nerve territory overgrowth. Mod Pathol. 2020 Mar;33(3):420-430. doi: 10.1038/s41379-019-0354-1. Epub 2019 Sep 3. PMID: 31481664.
2)
Filippidis A, Lidov H, Al-Ibraheemi A, See AP, Srivastava S, Orbach DB, Fehnel KP. Intracranial venous malformation masquerading as a meningioma in PI3KCA-related overgrowth spectrum disorder. Am J Med Genet A. 2021 Dec 2. doi: 10.1002/ajmg.a.62570. Epub ahead of print. PMID: 34854542.