**PIK3CA**, a hotspot for postzygotic mutations in nonhereditary overgrowth syndromes

**References**


Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome
Kurek et al. (2012)
Receptor tyrosine kinase (RTK)-PI3K-AKT pathway is an important growth-promoting pathway that harbors activating somatic mutations in many tumors (1). Recently, somatic mosaic activating mutations of AKT1 have also been associated with Proteus syndrome, which is characterized by segmental overgrowth of multiple tissues and susceptibility to the development of tumors (2). This suggests that disorders with similar overgrowth features may result from somatic mutations in RTK-PI3K-AKT pathway.

Sporadic and nonhereditary genetic disorders can be caused by somatic mosaic rather than germline mutations. CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal/spinal abnormalities, OMIM 612918) is a recently identified sporadic nonheritable genetic disorder characterized by asymmetric somatic hypertrophy and anomalies in multiple organs including vascular malformations and cutaneous and musculoskeletal abnormalities. On the basis of clinical similarities between CLOVES syndrome and other overgrowth disorders such as Proteus syndrome this syndrome would also arise from somatic mutations in the RTK-PI3K-AKT pathway. In this context, Kurek et al. investigated samples from CLOVES patients to identify postzygotic mutations and identified somatic mosaic mutations in PIK3CA in affected individuals (3).

To begin with, they extracted DNA and RNA from fresh or frozen affected tissues, and DNA from formalin-fixed lesional tissues from six CLOVES patients. They also extracted DNA from white blood cells of unaffected tissues (blood or saliva) from three patients. Applying parallel sequencing including whole exome sequencing (DNA from fresh/frozen tissue), custom-designed exome sequencing (DNA from fixed tissue), and RNA sequencing they sought mutations that were present at low frequencies (more than 5% of reads) in affected tissues. Exome sequencing revealed a missense PIK3CA mutation in every patient including p.Glu542Lys, p.Cys420Arg, and p.His1047Arg and mutant allele frequency ranged from 8% to 30%. However, the low mRNA expression of PIK3CA hindered the detection of these mutations in the RNA sequence data. The authors validated the presence of these mutations by employing gene-specific RT-PCR of PIK3CA as well as subcloning and Sanger sequencing the PCR amplimers encompassing the candidate mutations within the original tissues. DNA analysis of multiple affected tissue types dissected from an amputated lower limb of a patient with CLOVES syndrome revealed mosaicism for similar mutant allele (p.Cys420Arg) at all locations, suggesting that somatic PIK3CA mutations arise early during embryonic development.

PIK3CA encodes the catalytic subunit of PI3K and regulates the RTK-PI3K-AKT signaling pathway (Fig. 3a). Activating somatic mutations in PIK3CA including three mutations found in affected individuals with CLOVES syndrome have been described in various cancer types (4). Consistent with these observations Kurek et al. showed constitutional activation of PI3K-AKT pathway in CLOVES-affected individuals (Fig. 3b). However, the authors hypothesized that the low mRNA expression of PIK3CA in most cell types accounts for the low rate of malignant transformation in CLOVES syndrome. Also the low mutant allele frequency in various affected tissues would relate the pathophysiology of CLOVES phenotype to paracrine signaling from mutant to wild-type cells.

Mutations in PIK3CA could be associated with other overgrowth syndromes that exhibit similar features to CLOVES syndrome. Indeed, by screening the affected tissues from individuals with Klippel–Trenaunay syndrome for the two PIK3CA missense mutations (p.Cys420Arg and p.His1047Arg) Kurek et al. found mosaicism for the p.His1047Arg mutation in 20% of the patients.

This study attributed another overgrowth syndrome to somatic activation of PI3K-AKT pathway. Foremost, it highlights the importance of employing exome sequencing of anomalous tissues in defining causative somatic mutations in nonhereditary genetic
disorders. Since surgical debulking is one of the major treatments of segmental overgrowth disorders, finding activating \textit{PIK3CA} mutations in CLOVES-affected individuals brings hope for potential targeted therapy.

\textbf{Alireza Baradaran-Heravi}  
Department of Medical Genetics,  
Child and Family Research Institute, University of British Columbia,  
Vancouver, British Columbia, Canada  
e-mail: abara@cfri.ca