PIK3CA Activating Mutations in Facial Infiltrating Lipomatosis

Reid A. Maclellan MD, Valerie L. Luks BS, Matthew P. Vivero BA, John B. Mulliken MD, David Zurakowski PhD, Bonnie L. Padwa DMD, MD, Matthew L. Warman MD, Arin K. Greene MD, MMSc, Kyle C. Kurek MD

Background: Facial infiltrating lipomatosis (FIL) is a rare, congenital, non-heritable, disorder characterized by hemifacial soft-tissue and skeletal overgrowth, precocious dental development, macrodontia, hemimacroglossia, and mucosal neuromas. It has been hypothesized that FIL is caused by a somatic mutation, with regional expression, that arose during embryonic development. The purpose of this study was to search for causative somatic mutations in patients with FIL by using massively parallel sequencing.

Methods: Human FIL tissue was obtained prospectively from 6 patients during a clinically-indicated procedure and stored frozen. DNA was extracted from these specimens to produce massively parallel sequencing libraries that were enriched for coding sequences from genes involved in pathways that control cell growth using targeted capture. We massively parallel sequenced the enriched libraries and analyzed the sequence data for mutations that appeared to be mosaic and unique to the affected tissue.

Results: We identified a different missense mutation in PIK3CA in each patient's affected tissue. Two patients had a nucleotide transition that changed a histidine to an arginine codon at the amino acid residue 1047 (p.H1047R), the other patients had different amino acid mutations: p.H1047L, p.E453K, or p.E542K. Each mutation is predicted to significantly increase enzymatic activity. Filtering reduced the fraction of targeted basepairs containing variant reads to ~0.008%, which enabled us to identify causal missense mutations in each affected tissue sample. The frequency of mutant cells in the affected tissue ranged from 12% to 68%, compatible with their representing somatic mosaic rather than germline mutations.

Conclusions: Affected tissue from individuals with facial infiltrating lipomatosis contains PIK3CA mutations that have previously been reported in cancers and in affected tissue from other non-heritable, overgrowth disorders including CLOVES syndrome, Klippel-Trenaunay syndrome, hemimegalencephaly, fibroadipose overgrowth, and macrodactyly. Because PIK3CA encodes a catalytic subunit of PI3K, and in vitro studies have shown that the overgrowth-associated mutations increase this enzyme’s activity, PI3K inhibitors currently in clinical trials for patients with cancer may have a therapeutic role in patients with facial infiltrating lipomatosis. The strategy we employed to identify somatic mutations in patients with facial infiltrating lipomatosis is applicable to other somatic mosaic disorders that have allelic heterogeneity.

Disclosure/Financial Support
None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.