

Polyostotic non-ossifying fibromas in oculoectodermal dysplasia harbor activating mutations in KRAS

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Oculoectodermal syndrome (OES) is a rare disease characterized by a combination of congenital scalp lesions and ocular dermoids, with additional manifestations including polyostotic non-ossifying fibromas (NOF) and giant cell granulomas of the jaw. The bone phenotype of OES is variable but often severe. We recently demonstrated a mosaic pattern of somatic missense alterations in KRAS NM_033360.3(KRAS):c.38G>A resulting in p.Gly13Asp (i.e. KRASG13D), and NM_033360.3(KRAS):c.57G>C, p.Leu19-Phe alteration (i.e. KRASL19F) in 2 non-related OES subjects. The highest allelic frequencies of KRAS alterations (>40%) were demonstrated in three distinct anatomic sites of NOF involvement between the 2 subjects. The histopathology of these lesions was consistent with sporadic NOF's as confirmed by a board certified musculoskeletal pathologist. Tissues enriched in KRAS mutant alleles exhibited upregulated ERK and STAT3 phosphorylation (Western Blot; Immunohistochemistry) when compared to KRAS wild type controls. The observed deregulation of RAS/MAPK signaling confirms a shared molecular pathogenesis between the polyostotic NOF's observed in OES and those that arise in the setting of other RASopathies such as Neurofibromatosis Type1.