Molecular Analysis Identifies a Potential Epigenetic Role for AP-2α in Branchio-Oculo-Facial Syndrome

Hong Li, Trevor Williams

Department of Craniofacial Biology and Cell and Developmental Biology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO

Human Branchio-Oculo-Facial Syndrome (BOFS) is an autosomal-dominant trait caused by mutations in *TFAP2A*, the gene encoding transcription factor AP-2α. BOFS commonly presents with facial clefting, microophthalmia, and branchial skin anomalies, but expressivity is variable and there are no clear genotype:phenotype associations. We have previously demonstrated that the various BOFS mutations result in dominant negative versions of the AP-2α protein, with affects on the affinity and kinetics of DNA binding. We have now extended these studies by generating mouse models of human BOFS by conditionally knock-in of human patient mutations into the endogenous mouse *tfap2a* locus. The BOFS mouse models recapitulated the phenotypes seen in human patients, particularly variable cleft lip, cleft palate and nasolacrimal duct obstruction and revealed potential defects in thymus formation that have not been reported in human. These findings indicate that the *TFAP2A* mutations do act in a dominant negative manner *in vivo*, but also demonstrated that the same variable expressivity was also present in the mouse models as observed in human BOFS. We have now begun to probe the underlying cause of the variable clefting phenotype by examining the molecular and cellular behavior of AP-2α protein *in vivo*. Our results indicate that AP-2α may have an epigenetic function in controlling gene expression and the cell cycle that is disrupted by the various human BOFS mutations.