Tissue specific redundancy of TFAP2 family members during craniofacial patterning

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Transcription factor activator protein 2 (TFAP2) is a key regulator of craniofacial development, highlighted by the fact that mutations to two family members, TFAP2A and TFAP2B, result in syndromic disorders in humans that include craniofacial dysmorphisms (BOFS and Char syndrome, respectively). In addition, TFAP2 proteins likely contributed to the emergence of neural crest (NC), a key stem-cell population that emerges from the non-neural ectoderm (NNE) during development and attributed to generating the “new head” observed in vertebrates. Although a variety of TFAP2 family members are expressed robustly in both the NC and NNE during development, tissue specific knockouts have resulted in subtle craniofacial defects in animal models. In an effort to better understand the potential for redundancy in masking the functional role of TFAP2 paralogs in these two tissues (i.e. the NNE and NC) we have systematically deleted two family members simultaneously in either the NC or NNE during craniofacial development. Focusing on TFAP2A and TFAP2B, we find striking perturbances in normal craniofacial development, including midface hypoplasia, mimicking to some extent frontonasal dysplasia, upon deletion in the NC, and major patterning defects upon deletion in the NNE. Molecular profiling of the facial prominences in both models identifies key genes and pathways presumably co-targeted either directly or indirectly by TFAP2A and TFAP2B during craniofacial development, including unique targets in either the upper or lower face. Currently, biochemical analysis is being utilized to further uncover this gene-regulatory-network guiding proper facial morphogenesis. Collectively, these findings should provide clues into the molecular pathology associated with BOFS and Char syndrome as well as the role of TFAP2 proteins in the evolution of the vertebrate face.