The development of the face depends on the regionalization of neural crest precursors into distinct dorsal and ventral domains. Previous research has shown that Endothelin 1 (Edn1) is required for patterning the ventral face, in part by regulating Dlx expression; however, little is known about the factors required for development of the dorsal face. We have recently identified a mutation in the zebrafish gene jag1b that results in dorsal-specific defects. In jag1b mutants, we observe an expansion of Dlx genes into the dorsal domain, Jagged is one class of ligands for Notch receptors. Here we show that overactivation of the Notch pathway results in loss of ventral genes and corresponding defects in the ventral facial skeleton, further supporting a role of Jagged-Notch signaling in promoting dorsal facial identity. In addition, we find an autoregulatory loop of jag1b and notch2 expression that propagates in a dorsal to ventral wave of Notch activity during facial development. Based on these results, we propose a model in which dorsal–ventral facial identities are specified by dynamic interactions between a wave of Notch signaling arising dorsally and a gradient of Edn1 signaling arising ventrally. In our model, expression of jag1b localizes Notch activity to dorsal skeletal precursors. How then is jag1b expression established dorsally? Here we show that the endoderm is required for jag1b expression. Moreover, as the endoderm expresses Fgf5s, we next investigated the role of Fgf signaling in patterning. Using a transgenic to block Fgf signaling at patterning stages, we observe a transformation of dorsal structures to a ventral identity, a defect similar to that observed in jag1b mutants.

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Program/Abstract # 491
Hand2 loss leads to aglossia from failure to repress Dlx5/6
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Lower jaw development is a complex process orchestrated by signaling cascades that are regulated temporally and spatially and are constantly refined through permissive and inhibitory signals. We have previously shown that endothelin-A receptor (Ednra) signaling is crucial for establishing the identity of cranial neural crest cells (NCCs) in the mandibular pharyngeal arch through a mechanism that involves Dlx5 and Dlx6. Dlx5/6 in turn induce expression of the gene encoding the basic helix–loop–helix transcription factor Hand2. While this pathway places Hand2 at the center of a complex signaling cascade, little is known about the function of Hand2 in mammalian facial development because Hand2 is expressed in the pharyngeal arch region and later appears in the pharyngeal arches including a loss of cartilage and dermal bone. A loss of Hand2 results in defects in posterior pharyngeal arches including a loss of cartilage and dermal bone. A reduction in Fgf and retinoic acid signaling alters prdm1 expression suggesting that prdm1 is operating via these signaling pathways to pattern the posterior craniofacial skeleton. Finally, loss of prdm1 results in a reduction in proliferating cells suggesting that the cartilage defects may be due to a reduction in the number of NCCs. Future experiments will further determine the interactions between prdm1 and other known craniofacial genes as well as the function and tissue specific requirement for prdm1 during craniofacial development.

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prdm1 is required for zebrafish craniofacial development
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Defects in neural crest cell (NCC) differentiation result in many human congenital birth defects. A better understanding of cell fate determination, migration, and differentiation of NCCs during formation of the craniofacial skeleton is an important step towards developing approaches to prevent and repair human NCC-associated birth defects. We focused on the role of the transcription factor prdm1 in the differentiation of NCCs into the craniofacial skeleton. It does not appear that prdm1 is required for NCC migration but beginning at 16 hpf and continuing through 56 hpf, it is expressed in the correct temporal and spatial pattern to be involved in the differentiation of craniofacial structures. During early craniofacial development, prdm1 is expressed in the pharyngeal arch region and later appears to be expressed in an endodermal pouch, the otic vesicle, and pharyngeal teeth. A loss of prdm1 results in defects in posterior pharyngeal arches including a loss of cartilage and dermal bone. A reduction in Fgf and retinoic acid signaling alters prdm1 expression suggesting that prdm1 is operating via these signaling pathways to pattern the posterior craniofacial skeleton. Finally, loss of prdm1 results in a reduction in proliferating cells suggesting that the cartilage defects may be due to a reduction in the number of NCCs. Future experiments will further determine the interactions between prdm1 and other known craniofacial genes as well as the function and tissue specific requirement for prdm1 during craniofacial development.

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