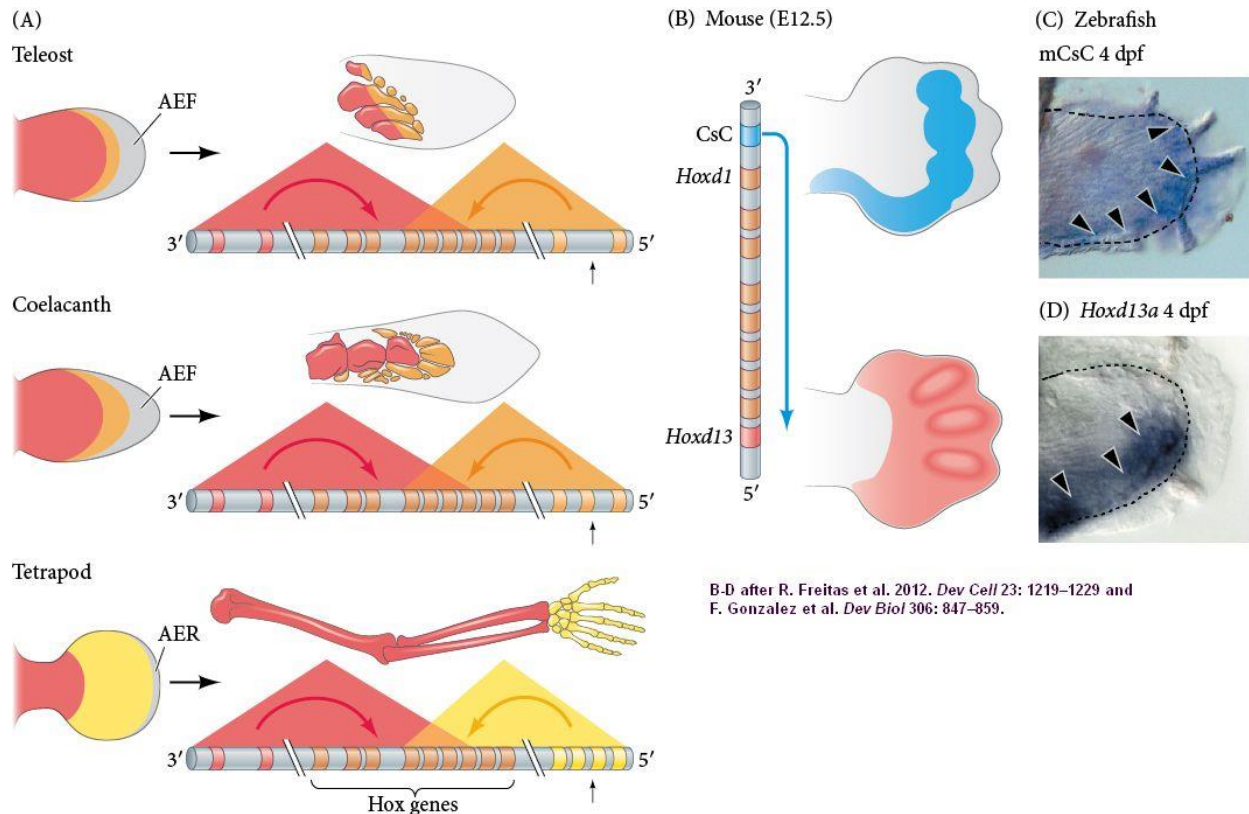


Homology Between the Limb Buds of Fish and Tetrapods

The fish fin bud is homologous to the limb bud and similarly has progress zone mesenchyme and an overlying apical ectodermal ridge (AER). However, after proximal patterning of the stylopod, the AER of the fin bud changes into an apical ectodermal fold (AEF) which promotes fin ray development as opposed to digits (Figure 1A). One hypothesis suggests that potential developmental delays in this AER-to-AEF transition would permit longer exposure to distal signals from the AER, enabling the progress zone mesenchyme to become increasingly permissive to autopod fates (digits). Moreover, changes in the spatial and temporal pattern of distal Hox genes may be responsible for the evolution of the tetrapod hand from the distal fin region of ancient lobe-finned fish (Schneider and Shubin 2013; Freitas and Gómez-Skarmeta 2014; Zuniga 2015). Increased numbers of *cis*-regulatory enhancers associated with the *Hoxa/d* clusters could provide one mechanism for heritable adaptation of the autopod. In further support of this model, researchers have identified both conserved enhancers (the global control region, or GCR, and CsB) and tetrapod-specific enhancers (CsS) that are associated with early (proximal) and later (distal) Hox gene expression. In fact, mouse CsS enhancers can functionally drive reporter expression in transgenic zebrafish embryos similarly within the distalmost mesenchyme (Figure 1B-D; Freitas et al. 2012).



After I. Schneider and N. H. Shubin. 2013. *Trends Genet* 29: 419–426; J. M. Woltering et al. 2014. *PLoS Biol* 12: e1001773/CC BY 4.0; and A. Zúñiga. 2015. *Development* 142: 3810–3820.

B-D after R. Freitas et al. 2012. *Dev Cell* 23: 1219–1229 and F. Gonzalez et al. *Dev Biol* 306: 847–859.

FIGURE 1 A) Schematic representations of the limb buds, adult limb structures, and the *Hoxd* gene cluster with associated 5' and 3' cis-regulatory enhancers of a teleost (zebrafish), hypothetical coelacanth, and human. In this illustration of the limb buds, the proximal and distal mesenchyme tissues are red and orange/yellow, respectively, and the apical ectodermal fold and ridge (AEF and AER) are gray. In the adult limbs, the formation of fin radials is seen in both teleost fish and coelacanths (red for proximal, orange for distal, gray for the dermoskeleton), whereas the digits of the autopod are present in humans (yellow). Adaptation of the 5' cis-regulatory regions of Hox genes may underlie autopod evolution. (B–D) The tetrapod-specific cis-acting regulatory element (CsC) for mouse *Hoxd13* drives similar expression in the zebrafish distal fin bud. (B) *Hoxd13* is positioned downstream and is responsive to the actions of the CsC enhancer in the distal mouse limb. (C) In the zebrafish fin, this same mouse CsC enhancer can drive reporter gene expression (mCsC:GFP; blue, arrowheads) in the distal limits of the endoskeletal territory (dashed line). dpf, days postfertilization. (D) This mCsC:GFP expression pattern in the zebrafish fin is spatially similar to the endogenous expression pattern of *Hoxd13a* (blue, arrowheads), suggesting the CsC could be a conserved enhancer of Hox gene regulation. (A after Schneider and Shubin 2013; Woltering et al. 2014; Zuniga 2015; B–D after Freitas et al. 2012.)

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