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Influence of *Hoxa11* and *Hoxd11* on Calcaneus Growth and Ossification

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Abstract

Hox genes are key developmental patterning genes that impact segmental identity and skeletal patterning. While Hox11 genes are known to be expressed around the developing calcaneus bone of the ankle, previous studies on mice with Hox11 mutations have indicated that calcaneus morphology is not affected until both *Hoxa11* and *Hoxd11* are knocked out, at which point the calcaneus and talus fail to form. The pisiform bone, a



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wrist bone that is paralogous to the calcaneus, exhibits substantial morphological and growth plate alterations with Hox11 mutations. We have previously shown that some length differences are present in the adult calcanei of mice with *Hoxa11* and *Hoxd11* loss-of-function mutations. The present study investigates whether or not the calcaneus growth plate is altered by *Hoxa11* and *Hoxd11* loss-of-function mutation. We conducted histological analysis of the calcaneus growth plate in juvenile mice with *Hoxa11* and *Hoxd11* loss-of-function mutations and compared them to ossification patterns observed in whole-mount specimens that were cleared and stained with alizarin red and alcian blue to visualize bone and cartilage, respectively. Histological analysis reveals that early calcaneus growth plates preserve the hypertrophic and proliferative growth plate zones. This is in contrast to the pisiform and likely a result of Hoxc gene expression in the hind limb but not the forelimb. The shape of the epiphyseal cartilage, however, differs greatly in mice with a combined three loss-of-function alleles between *Hoxa11* and *Hoxd11*. In these mice, the calcaneus epiphyseal cartilage is conical shaped with an elongated region of reserve zone chondrocytes. The ossification front and calcaneal tendon insertion are also altered compared to wild type specimens. The first evidence of calcaneal epiphysis ossification appears at P9 in some Hox11 mutant mice, while it typically appears at P11 in wild type specimens. By P17, the epiphysis appears to be larger in specimens with both *Hoxa11* and *Hoxd11* mutations compared to wild type. These results indicate that the calcaneus growth plate is more resilient to Hox11 mutations than the pisiform, but that the calcaneus exhibits morphological changes and evidence of altered ossification timing with fewer loss-of-function alleles than identified by previous studies.

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