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Differential Impact of *Hoxa11* and *Hoxd11* on Pisiform Ossification and Epiphysis Formation

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Abstract

Hox genes are key developmental patterning genes that impact segmental identity and skeletal patterning. Hox11 genes are known to impact wrist and ankle development and are expressed around the developing pisiform and calcaneus. These paralogous bones in the wrist and ankle are the only carpal and tarsal to form a growth plate in mammals, although humans have lost this

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growth plate and the associated primary ossification center in the pisiform. Loss-of-function mutations to *Hoxa11* and *Hoxd11* result in pisiform truncation and appear to also cause at least some disorganization of the growth plate cartilage; however, little is known about the nature of this disorganization or if ossification timing is impacted by Hox11 genes. The present study investigates the role of *Hoxa11* and *Hoxd11* in pisiform growth plate organization and ossification timing. We conducted histological analysis of the pisiform growth plate in juvenile mice with *Hoxa11* and *Hoxd11* loss-of-function mutations and compared them to ossification patterns observed in age- and genotype-matched whole-mount specimens that were cleared and stained with Alizarin red and Alcian blue to visualize bone and cartilage, respectively. Histological analysis reveals a dosage-dependent impact of Hox11 mutations on pisiform ossification to both the primary and secondary ossification center. As the number of Hox11 mutation alleles increase, less bone is present in the early primary ossification center compared to age-matched specimens. In specimens with three loss-of-function alleles, no trabeculae or growth plate organization are visible at P9, when both are well established in wild type specimens. Cleared and stained specimens indicate a possible pseudo epiphysis forming with *Hoxd11* mutation, while *Hoxa11* knockout specimens have not formed any visible epiphysis or calcification by P9. These results indicate that ossification timing and patterns, along with growth plate organization, are affected by Hox11 mutations during early pisiform ossification. Furthermore, *Hoxa11* and *Hoxd11* alter the pisiform epiphysis differently, suggesting that each plays a specific role in formation of the ossification front and epiphysis ossification either by influencing timing, ossification progression, or both. Further work is needed to understand the mechanisms

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> Further work is needed to understand the mechanisms by which Hox genes impact ossification patterns and timing, as well as the differential roles of *Hoxa11* and *Hoxd11* in growth plate organization and epiphysis formation.